THE American JOURNAL OF Surgery

OCTOBER 1956

THURSTON SCOTT WELTON, M.D., EDITOR

Fracture of the Spine

Surgery for Cancer of the Breast

Infected Wounds and Chronic Sinus Tracts

SIXTY-FIFTH YEAR OF PUBLICATION

OCTOBER 1956

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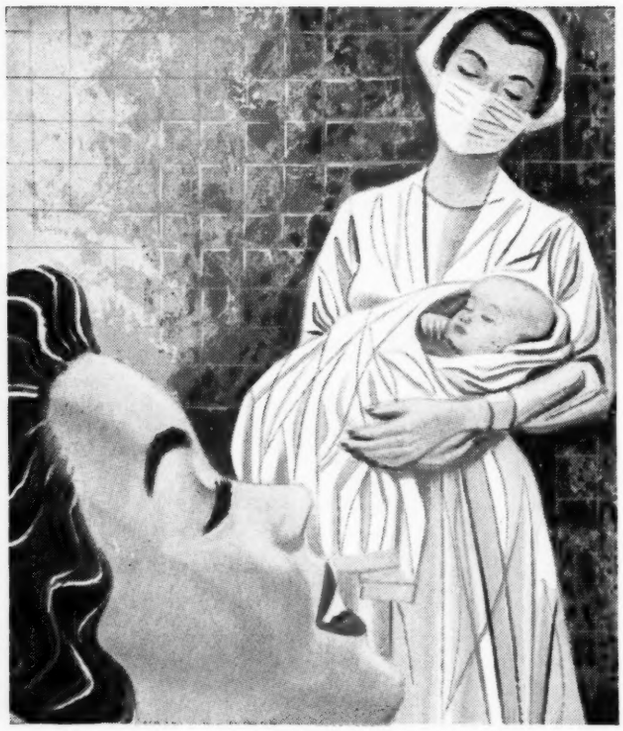

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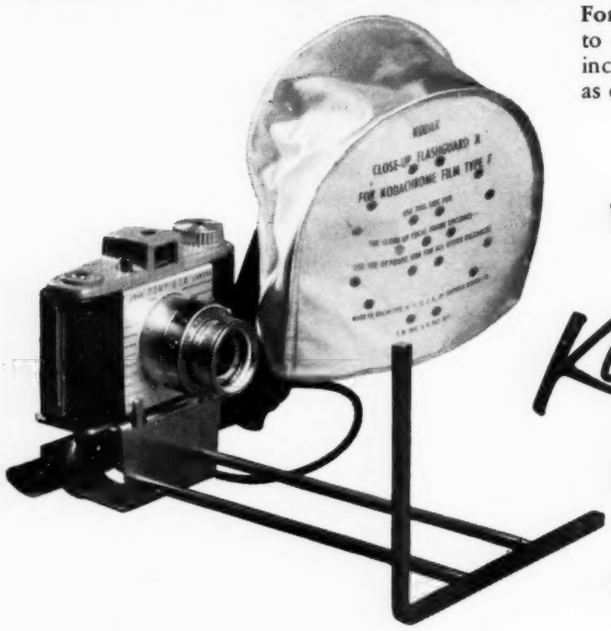

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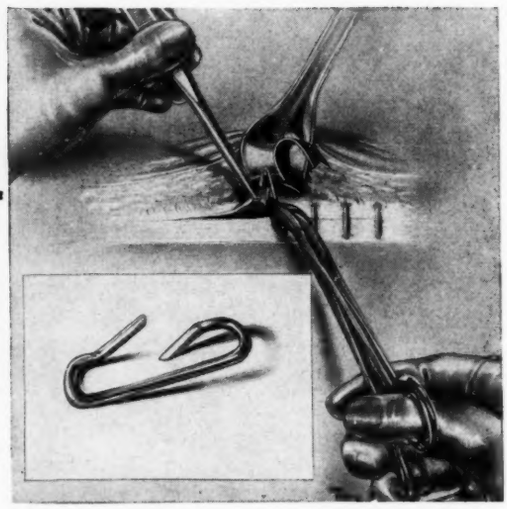

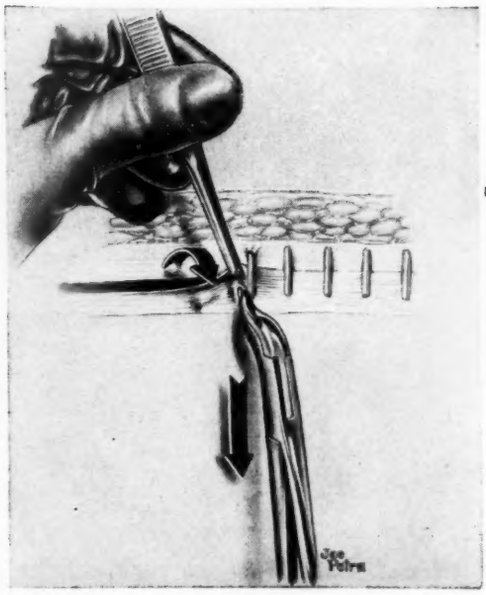

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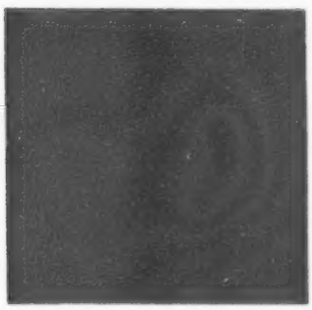

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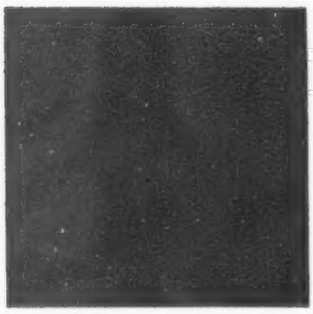

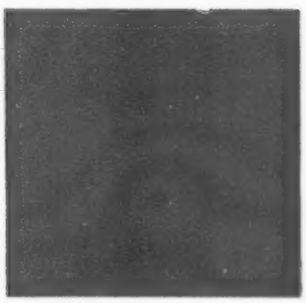

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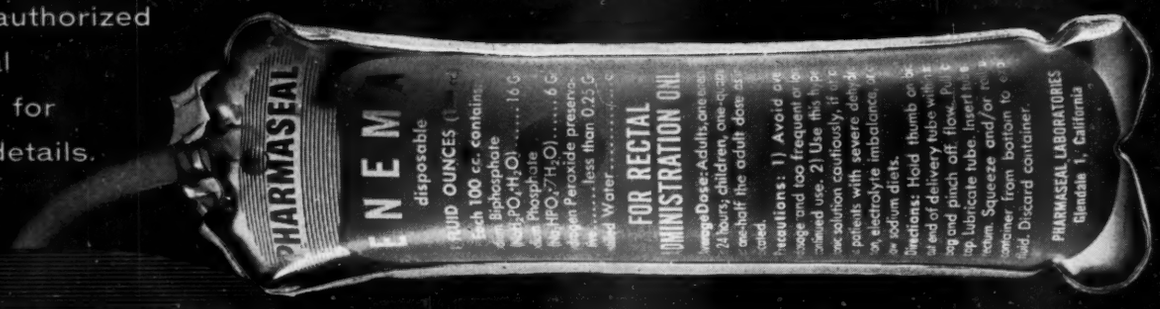

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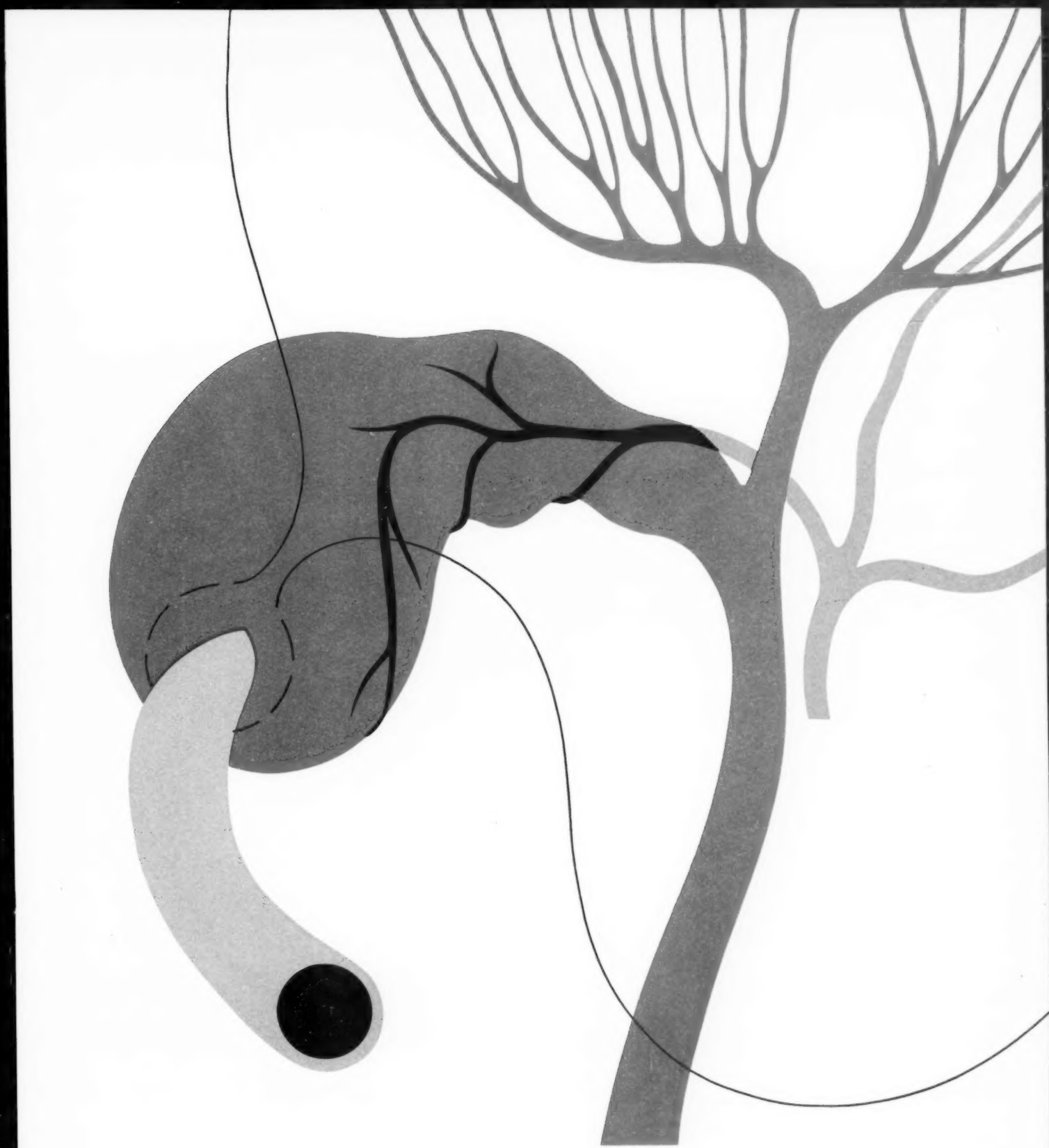

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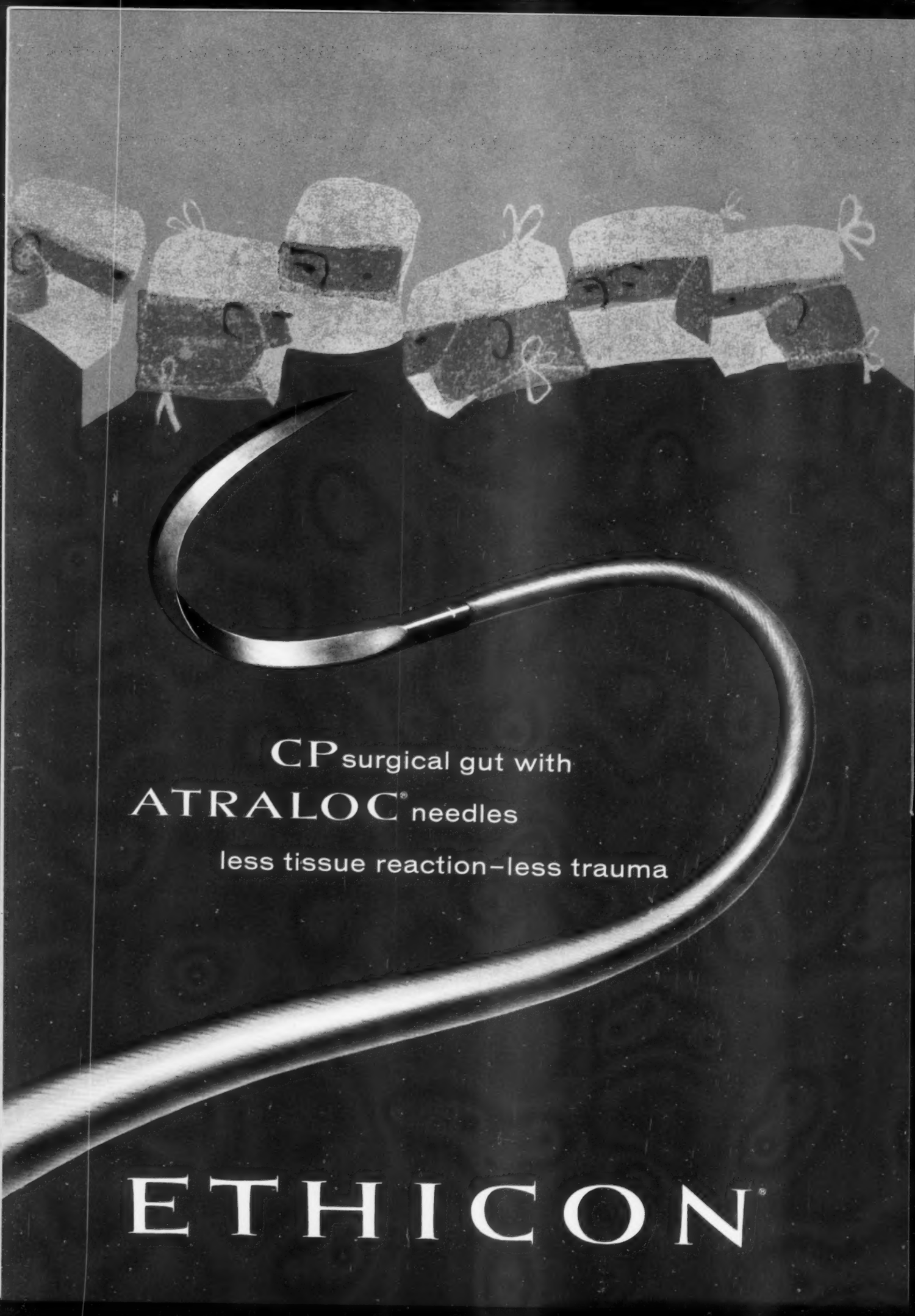
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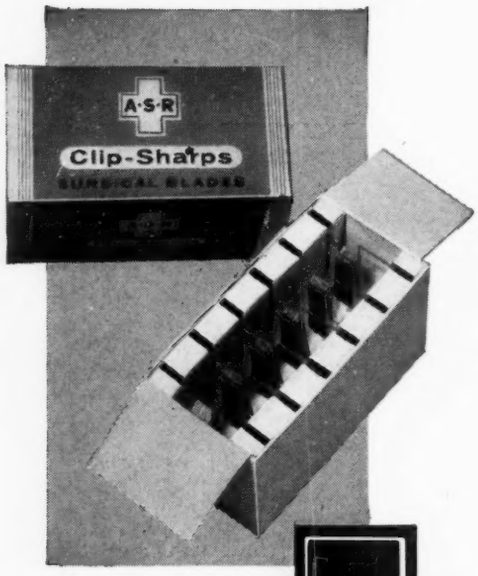

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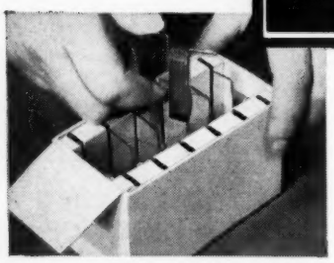

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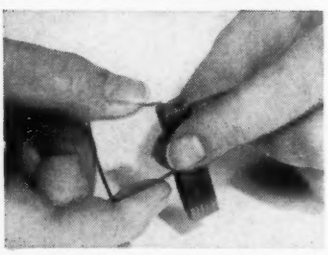

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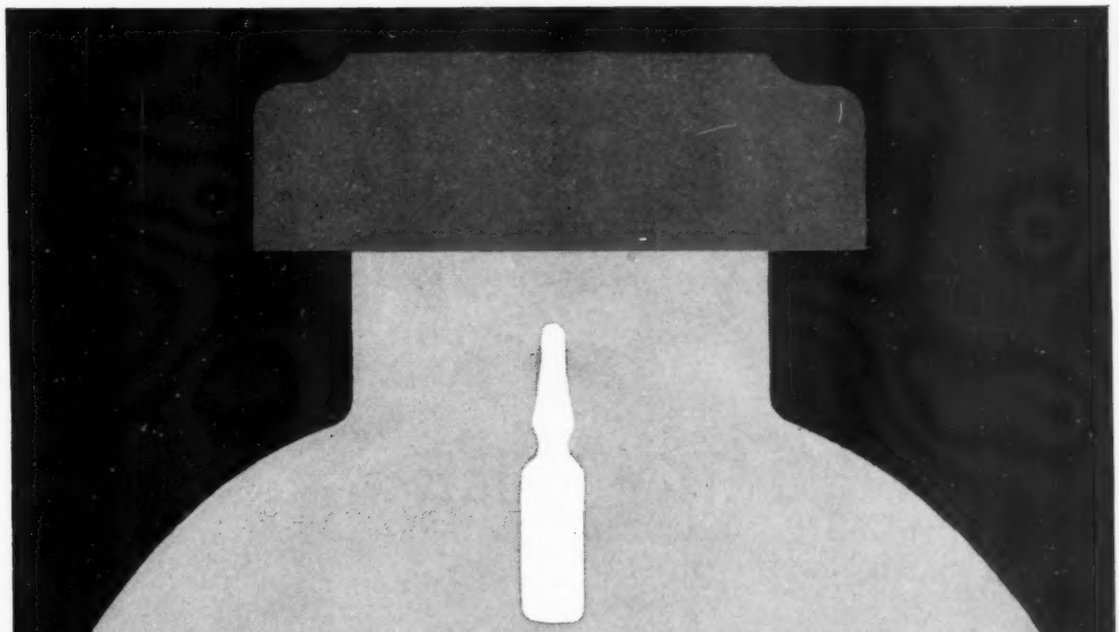

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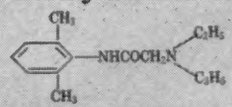

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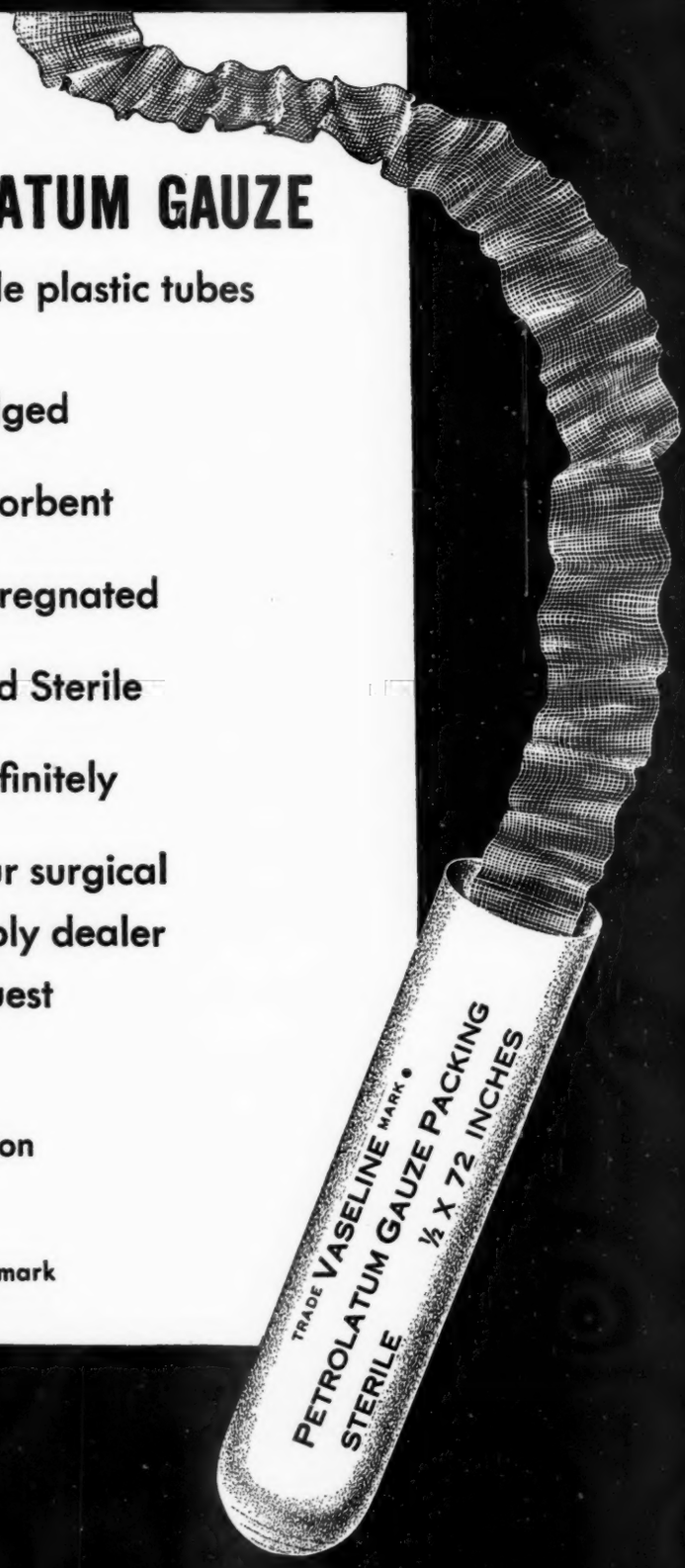

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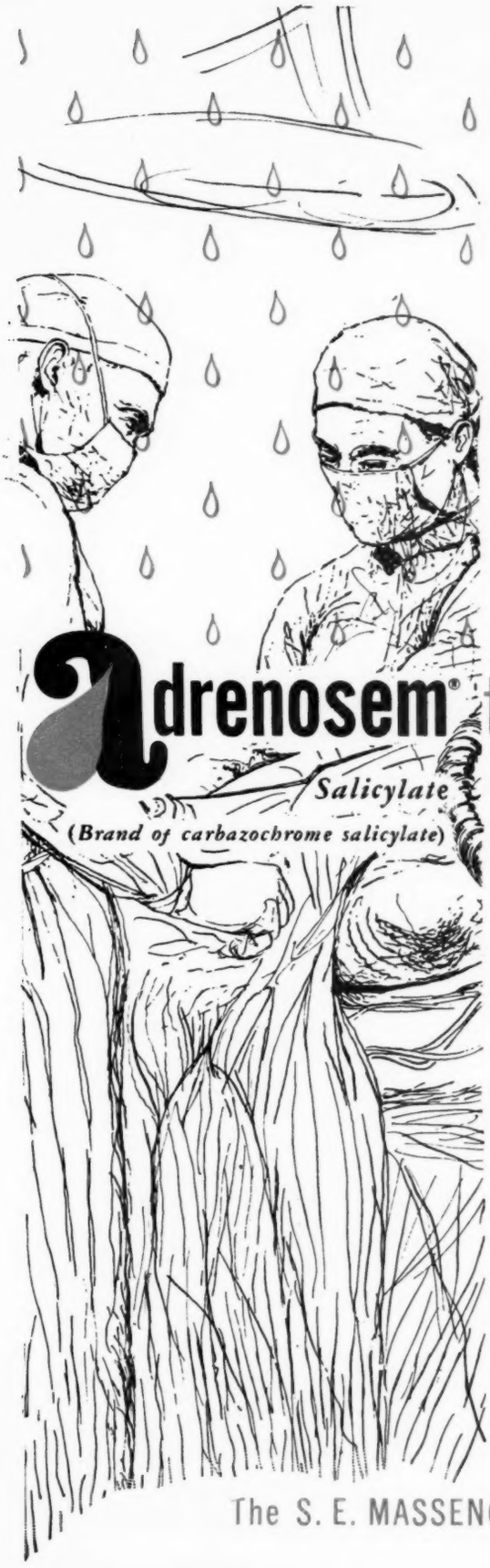

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1. *Bacala, J.C.: The Use of the Systemic Hemostat Carbazochrome Salicylate, West. J. Surg. 64:88 (1956).*

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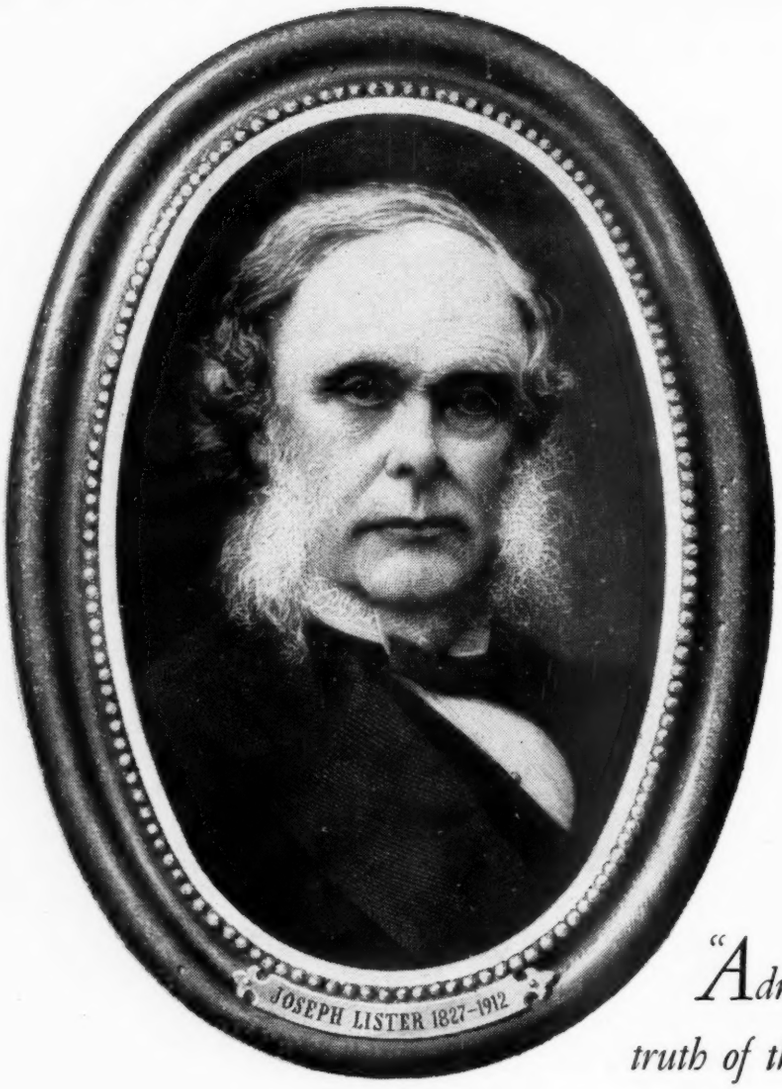

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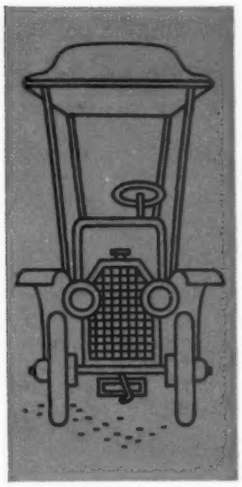

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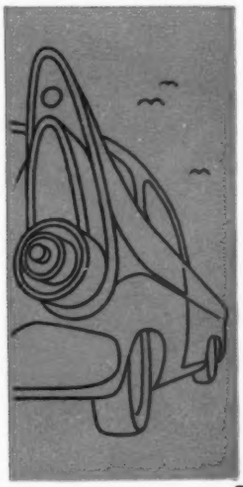

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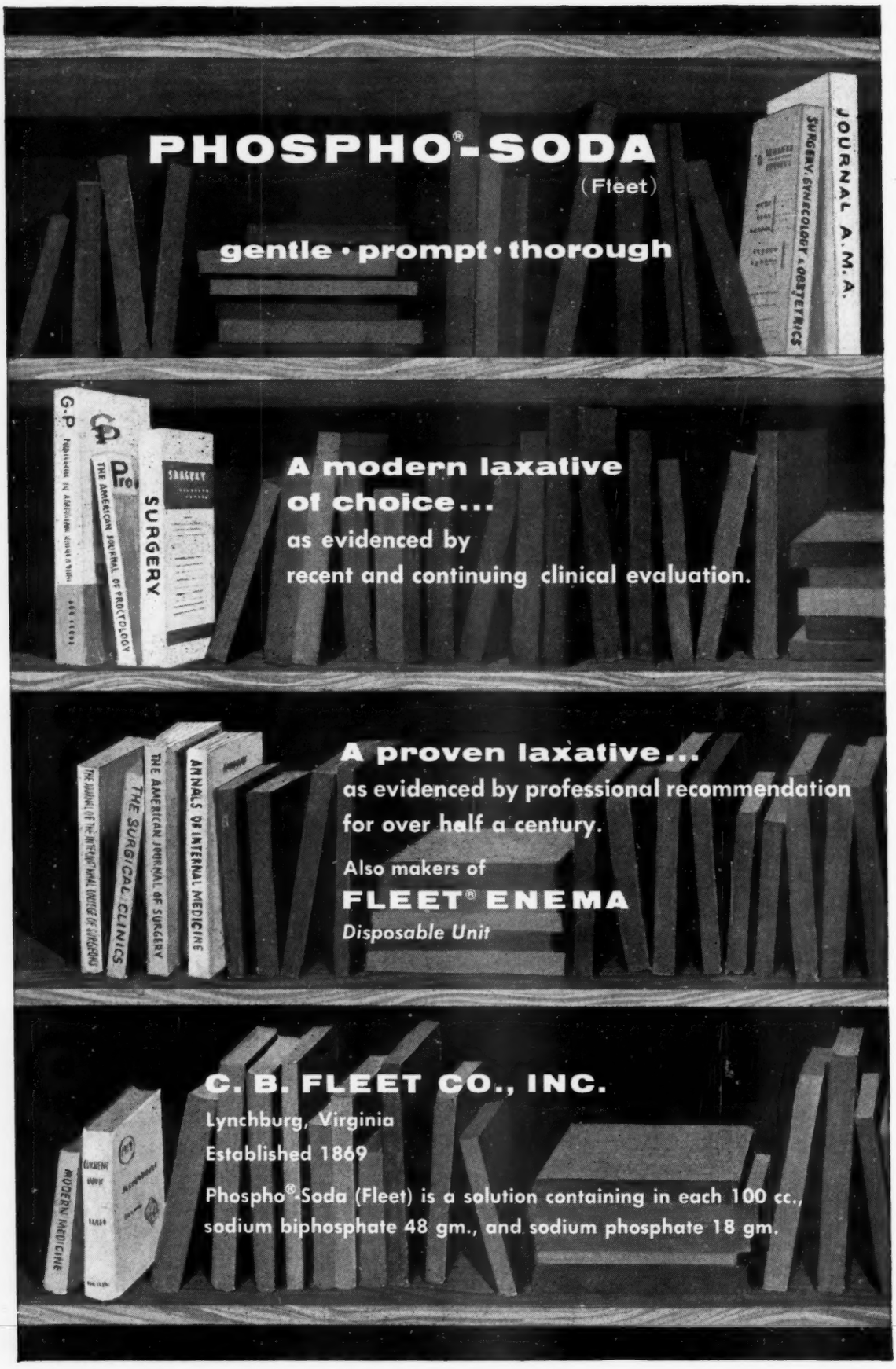
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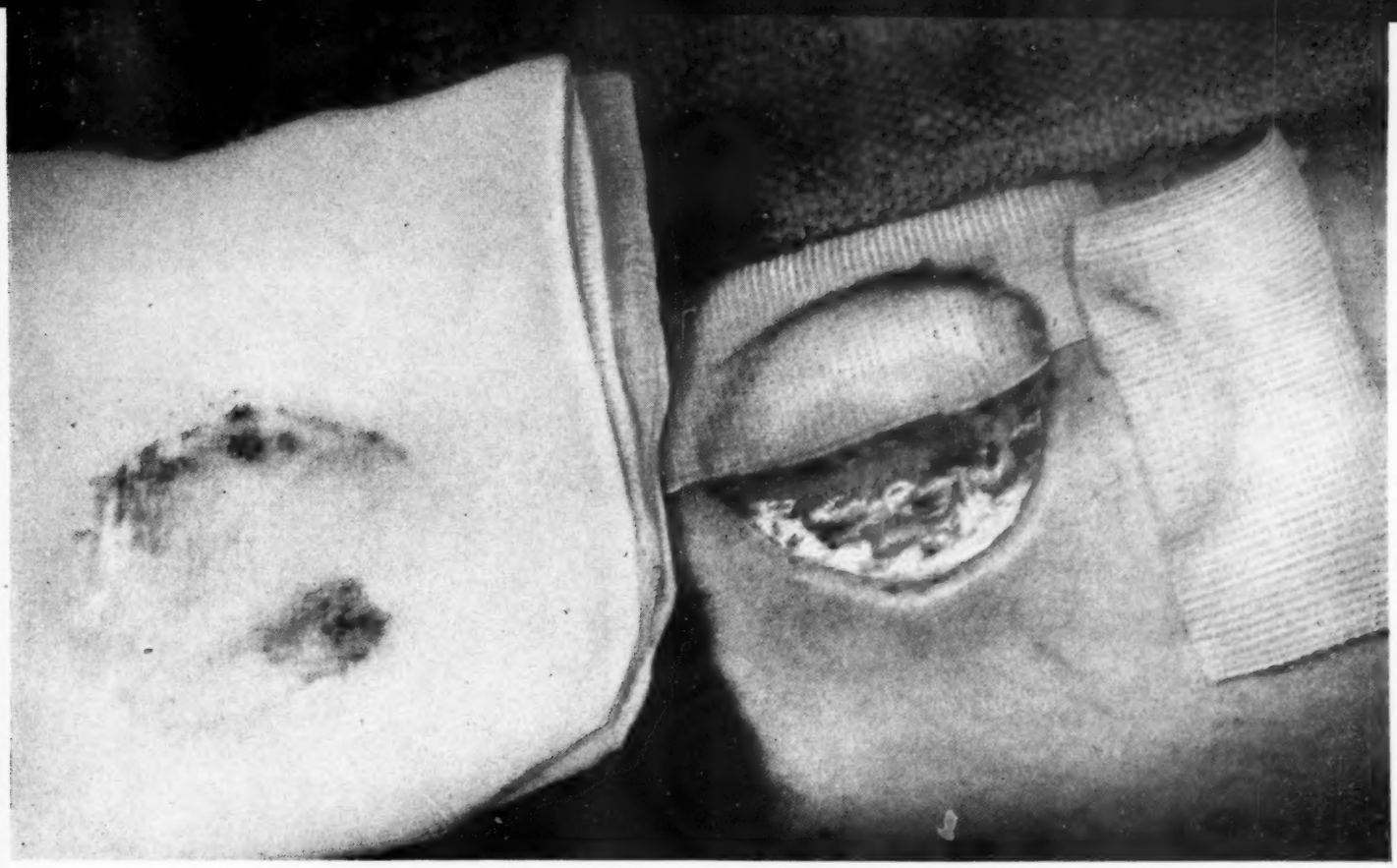

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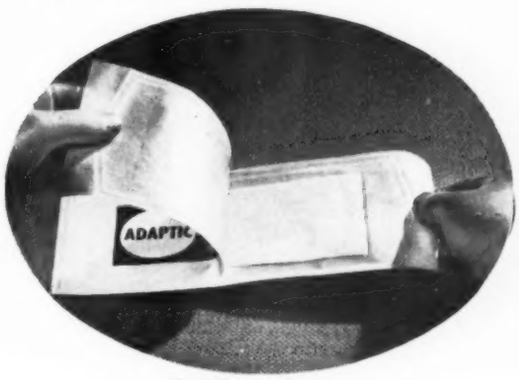

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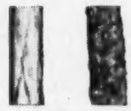

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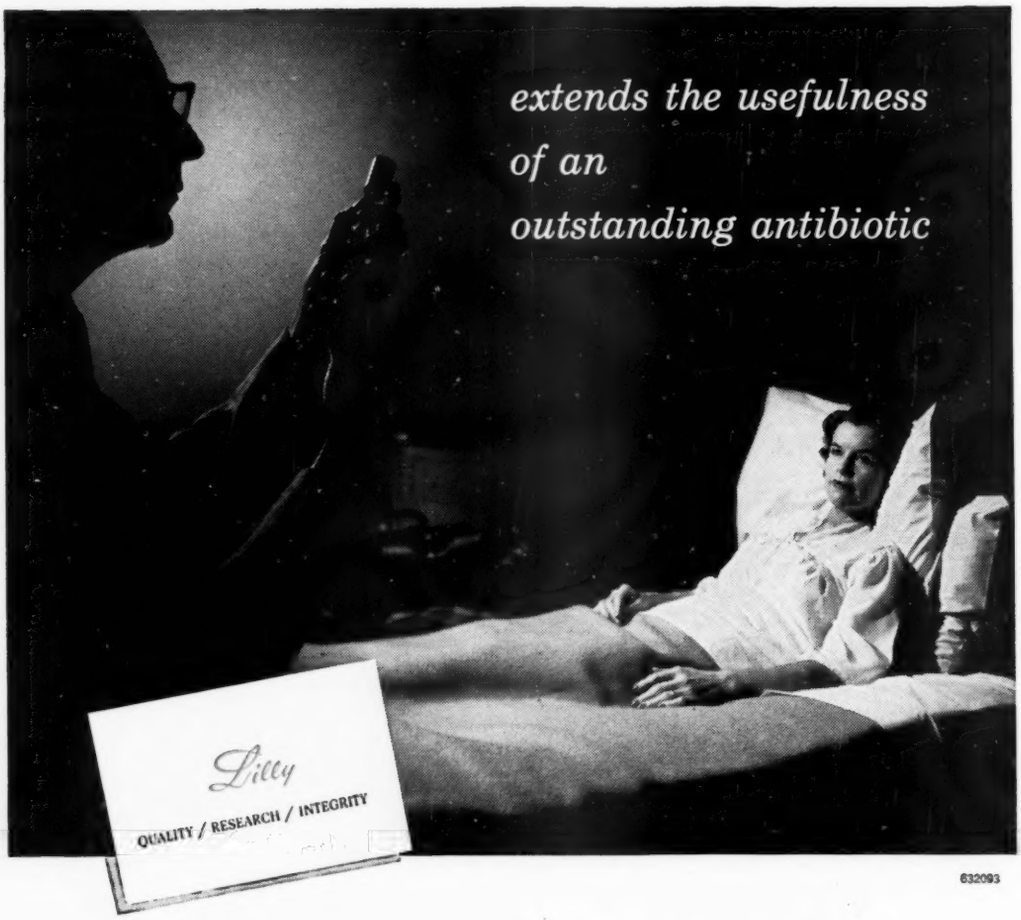

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The American Journal of Surgery

VOLUME 92 OCTOBER 1956 NUMBER FOUR

EDITORIAL

Basis for Choice of Operation for Cancer of the Breast

A VALUABLE contribution that senior members on a hospital staff can make lies in the teaching of the art of surgery as opposed to the science, and that philosophic and humane approach to the patient which can come only from long experience. In no field is there a greater need for such an attitude than in the treatment of cancer of the breast.

The final outcome in most cases of carcinoma of the breast is governed by the type of growth and host resistance factor rather than the time of operation or the type performed. There is little doubt that an operation for cancer should be sufficiently radical to give the greatest possible hope for cure. However, when this cannot be attained and the procedure becomes so radical that it results in excessive immediate mortality, or is followed by such disability and morbidity as to make life unbearable, one should assess values carefully.

Cancer probably begins with alteration in biologic activity in a small nest of cells, possibly in a single cell or, as some believe, multicentrically in a limited area. These abnormal cells multiply gradually, overcome the restraining influence of surrounding cells and tissue (host resistance) and the regulating forces that govern normal cells, invade surrounding tissue, and proceed in their lawless growth.

The basic surgical concept of an acceptable operation for cure of carcinoma of any organ of the body encompasses two factors. The first is that the local lesion should be resected with an adequate margin of apparent normal tissue about it. The second factor is that as extensive a resection of the field of lymphatic drainage of the carcinoma as is surgically and anatomically practical must be carried out.

When these two factors are applied to operable carcinoma of the breast, it is obvious that there can be no adequate local excision of the local lesion such as one can perform, for example, in carcinoma of the colon. The pathology of carcinoma of the breast from its inception would make local excision most inadequate; however, patients have been known to be free of disease for many years after simple local excision of a lesion. Simple mastectomy, however, could be considered in operable cases as resection of the local lesion with an adequate margin of apparently normal tissue around it. The removal of accessible axillary nodes could also be accomplished without much difficulty. This does not imply that all involved tissue would then be removed, because this would be anatomically impossible with the most aggressive and honest surgical therapy. Extension of the surgically inaccessible disease must be treated by adequate radiation therapy to all fields of lymphatic spread that cannot be excised.

The second factor, namely that of extensive resection of the field of lymphatic drainage, is the point of dispute that requires further discussion.

The lymphatic drainage of the breast is rich and replete with plexuses, so that the direction of spread of malignant cells through these channels is understandably unpredictable and fortuitous. Drainage is generally toward the

skin surface where a subcutaneous plexus of lymphatic vessels permits the cells to be carried in almost any direction. The cells may migrate medially to the internal mammary nodes or laterally to the axillary nodes. They may even migrate to inguinal nodes. These migrations may require months or years. Periods of quiescence are followed by fresh migrations. Skin nodules are commonly observed in the vicinity of the lesion in advanced cases or they may appear years after mastectomy. These so-called recurrences simply indicate macroscopic extension of disease that was present but not removed at the time of operation.

The lymphatic trunks that converge toward regional lymph nodes provide another method for spread of cancer of the breast. The spread occurs superiorly toward the axilla and supraclavicular nodes, medially toward the internal mammary group and mediastinal nodes, and inferiorly through the linea alba into the abdomen. The exhaustive studies of many qualified investigators have revealed that these paths of dissemination are never predictable. The lesion can spread to the supraclavicular nodes without involving the axilla; it may spread directly into the internal mammary group and mediastinum without involving the axilla; it could extend directly into the chest, over to the other breast and axilla, into the abdomen and even down into the inguinal nodes. When tumor cells invade a lymphatic vessel they can progress more rapidly in the form of a solid cord of cells.

Proliferation along lymph channels is not the only method of dissemination. Tumor cells also migrate, and like white blood cells they can work their way through the walls of capillaries and thereby spread by way of the blood stream. This method of dissemination can well explain the all too frequent case of a patient with a small lesion, no regional adenopathy and with distant metastases.

The principle upon which radical mastectomy was originally performed was that cancer of the breast generally would spread in an orderly fashion and in one direction, i.e., into the axillary nodes. It is obvious from the rather brief description of the lymphatic spread of this disease that this is not true in most of these patients; by the time the patient presents herself for therapy many of the other nodes are involved. Even the ultraradical procedures do not encompass all these avenues of spread in their surgical maneuvers. Removal of the breast, axillary nodes, supraclavicular nodes, internal mammary nodes and even part of the chest wall does not assure one of a cure. Halsted appreciated this soon after he became interested in this field of surgery.

The location of the lesion in the breast and the prediction of the involvement of a particular group of nodes is another point for emphasis in the choice of operation for carcinoma of the breast. Handly and Thackery have indicated that the internal mammary chain of nodes is involved in a high percentage of malignant lesions of the breast. Other investigators have proposed that the internal mammary group of nodes is more likely to be involved with a lesion in the medial quadrant of the breast, and they have devised ultraradical procedures to remove all involved tissue. On the other hand, Hutchinson found no correlation between the location of the lesion in the breast and the incidence of mammary node involvement in his study of eighty-one consecutive cases.

The scope and extent of operation has been evaluated by many. A most interesting recent report by Mayer and Smith indicated that in a group of 148 patients with cancer of the breast, treated in a small hospital, those operated upon by the more inexperienced group of surgeons, who used procedures that fell far short of the recognized radical mastectomy, did better and had a more satisfactory five-year survival rate than those operated upon by the more expert surgeons performing radical mastectomy. This, of course, is no reflection on those who perform radical mastectomy or an indictment of their surgical skill. However, it does seem to indicate that the more extensive procedures may be conducive to more rapid dissemination because they open more avenues for spread of disease. Mayer and Smith report a five-year survival rate of 57 per cent for patients who had simple mastectomy, while the rate for the patients with radical mastectomy was 49 per cent.

Many open-minded surgeons have realized the futility of heroic attempts and are now willing to consider the simpler methods of therapy. Some even go so far as to refuse surgery to patients with certain extensions of the disease who recently were considered operable. Although surgery is undoubtedly the best method available for certain very early localized lesions, the simpler procedures with ade-

quate postoperative radiation therapy seem to be a modality for treatment which has been proved to be adequate and statistically at least as good as radical mastectomy, without the postoperative morbidity and mortality that follow radical procedures. Reports in support of this are appearing in the literature with increasing frequency.

This change in the trend of thinking about surgery for cancer of the breast is not new, for Halsted himself realized the inadequacy of radical mastectomy. It was not long after the publication of his method of treatment that he attempted supraclavicular and mediastinal extensions of the operation. However, soon afterward he very wisely did not continue the ultraradical measures. I daresay that if Halsted were alive today he would probably discontinue the use of the operation that bears his name.

One cannot question the wisdom of those who, by training and experience, are especially taught to extend the scope of surgery, exploring all possibilities. However, they should not advocate that such procedures be adapted widely until time and experience have proved their worth. In treating carcinoma of the breast, the extended procedures have indeed proved futile and in fact most harmful.

Cancer of the breast has been considered incurable by many observers; since we cannot cure the patient, let us employ a modality of therapy that will do the least harm. I sincerely believe that simple mastectomy and possibly the removal of accessible axillary nodes, with a high standard of adequate postoperative radiation therapy, should be considered the procedure of choice in the treatment of this disease.

The choice of operation for cancer of the breast should be one that does the most good for the greatest number of patients, and not one that satisfies the criteria proposed by a surgeon. Perhaps this subject should be another item for serious consideration on the agenda of the audit committees of our institutions. Their good work could well be extended to the field of surgery of the breast. In that way the unnecessary morbidity and suffering that follow many of the unrequired radical procedures could be prevented.

I know that the simpler procedures obviously lack the radical character and quality of finality that must appeal to the heart of every keen surgeon. Nevertheless, we cannot ignore our moral obligations to the patients with this dreaded disease. One should go to great lengths to relieve pain and mental anguish and restore function, and thus make whatever time remains worth living.

THOMAS C. CASE, M.D.,
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SCIENTIFIC PAPERS

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THE débridement and healing of infected wounds resulting from trauma or surgery, especially when the wounds are of the chronic type, remains one of the annoying and trying problems of surgery. Even more difficult to treat are the narrow sinus tracts of a chronic nature which sometimes form deep cavities or long, constricted tracts. In the early stages of abscess formation simple drainage may be adequate; however, with more advanced or chronic infections this treatment is frequently unsatisfactory and extensive operations may be necessary to ensure satisfactory healing. The use of chemical agents for the cleansing and débridement of wounds is not new. For débridement Dakin's solution was used with great success, and in the not too distant past débridement using maggots was successful in refractory cases. Organic acids such as pyruvic and phosphoric acid[4,12,14] have been used to advantage in hastening the separation of burn eschars. Stimulation of healing by chemical means has been less satisfactory.

So-called enzymatic débridement of wounds primarily with streptokinase-streptodornase and trypsin has been found very useful by many investigators. Trypsin itself is an active enzyme which is proteolytic in nature, and streptokinase-streptodornase is a combination of enzyme activator and enzyme produced by certain strains of streptococci. Streptokinase activates plasminogen in the exudate to plasmin (fibrinolysin) which dissolves the fibrin in the wound. Streptodornase acts by lysing the sticky desoxyribonucleic acid which remains after the destruction of tissue and purulent cells. The use of these materials in chronic hemothoraxes and empyema,[10,17,18] chronic ulcers,[7,8,17] burns,[3,16] fistulous tracts[9] and surgical wounds[15] is commonly reported. Papain[5] has been used occasionally with success. More recently other enzyme products have been developed, including bovine plasmin[6] (fibrinolysin) and pancreatic desoxyribonuclease; as yet the effects of these substances have not been adequately studied. Both trypsin and streptokinase-streptodornase, the two more commonly used products, have certain disadvantages which will be discussed herein.

Since the effect of streptokinase-streptodornase is mainly that of the streptokinase which activates plasminogen to plasmin, it seemed desirable to use plasminogen itself which is now prepared by a reproducible

method. Since these enzymes act primarily by lysis of fibrinous exudate and removal of necrotic debris, there could be little reason to expect that they would hasten healing other than by decreasing infection and edema. In order to hasten healing it seemed theoretically desirable to add another enzyme, hyaluronidase. This enzyme acts on the hyaluronic acid of the intercellular substance, liquefying it and permitting the diffusion of nutrient substances and oxygen as well as antibiotics into the wound. Thus hyaluronidase may hasten healing. Our belief that these materials might be of value was further supported by our work on chronic ulcers secondary to varicose veins which has previously been reported.[13]

In some patients antibiotics were added to the enzyme mixture because of the belief that the local effectiveness of antibiotics given both locally and systemically could be enhanced by enzymatic débridement of intervening slough and that diffusion into these wounds could be increased with the aid of enzymes.

This article is a report of our experience with a number of infected postoperative wounds and sinuses, many of which had been refractory to the usual types of treatment for a prolonged period of time before the introduction of the enzyme treatment. These wounds therefore acted as their own controls.

MATERIALS

(1) Streptokinase-streptodornase (SK-SD) mixture (varidase®); 100,000 units SK and 25,000 units SD dissolved in 10 cc. of distilled water. (2) Plasminogen (profibrinolysin): Prepared from fraction III of human plasma by a modification of a previously reported method;[2] 35 mg. powder dissolved in 1,000 ml. of water; 10 cc. of this solution were activated with 0.5 cc. of SK-SD mixture. (3) Hyaluronidase* 150 T.R.U./ml. (4) Oxytetracycline (terramycin®) 25 mg./ml. (5) Bacitracin† 500 U./ml.

Thirty-one patients with granulating wounds or chronic sinuses of long duration were studied. Seven had abscesses of the breast (six chronic and one acute), three had persistent sinus tracts opening into large cavities, six had chronic smaller sinus tracts and fifteen had open granulating wounds.

* Diffusin,® 1,500 T.R.U./vial dissolved in 10 cc. distilled water. Furnished by the Ortho Pharmaceutical Corp., Raritan, N. J.

† Topitracin, 50,000 U./vial dissolved in 100 cc. distilled water. Drug (now owned by Reed & Carnrick) furnished by Commercial Solvents Corp., Terre Haute, Ind.

METHODS

The wound was irrigated with a saline solution to remove any loose debris. The freshly prepared enzyme solutions were then instilled into the wound after the patient had been placed in a position which would assure adequate contact of the materials with the wound surfaces. Following this procedure sterile gauze saturated with the enzyme solution was packed into the wound. Vaseline gauze was placed over this packing to act as a seal and was reinforced with dry sterile dressings. The period of immobility in the position of choice was limited to twenty to thirty minutes and the patient was then ambulated. Initially these dressings were used one or two times daily. As the wounds become cleaner, the number of treatments was reduced in some patients to one or two times a week.

Plasmin (fibrinolysin) was used for the initial débridement or cleansing of the wounds. When the granulation tissues were clean and pink, hyaluronidase was added to the plasmin or used alone. In some cases an antibiotic solution was added to the enzyme mixture in a ratio of 1:1.

RESULTS

1. *Abscesses of the Breast* (*Table I*). Seven patients with abscesses of the breast were treated. Five cases occurred postpartum and two were of unknown etiology. In six cases the abscesses had been incised and drained four to eight days before treatment was begun and presented open draining wounds containing much debris. Three of these patients were treated daily with enzymes and three patients were used as controls with daily saline irrigations and packs.

Two patients (Cases 1 and 2) were ideally treated with both plasmin and hyaluronidase, and their wounds healed in eleven and eight days, respectively. This contrasted with the three controls (Cases 5, 6 and 7), who had healing in eighteen, twenty-five and thirty-three days, an average of more than twice as long. One patient (Case 3) was started on the ideal treatment of plasmin and hyaluronidase, and it was noted that the wound was clean in twenty-four hours and was healing well at five days. At this time it was considered desirable to discontinue treatment with the enzyme

TABLE I

ABSCESSES OF BREAST

Case No., Sex and Age (yr.)	Type of Wound and Etiology	Previous Therapy			Duration* of Local Previous Therapy	Condition and Size of Wound at Onset of Enzyme Therapy	Local Treatment: Agent, Duration* and Frequency†				Total No. of Days until Healed	Concomitant Systemic Therapy	Comments
							Enzymes			Saline Only			
		Procedures	Systemic	Local			Drugs	In Hospital	In O.P.D.	In O.P.D.			
1, F, 21	Abscess of breast postpartum	Incision and drainage	Penicillin	Saline	7	Walls dirty, granulating, with moderate drainage; size 6 by 2 cm.	Plasmin and hyaluronidase	0	10	0	11	None	Clean granulations 24 hr.; drainage decreased rapidly
2, F, 18	Abscess of breast postpartum	Incision and drainage	Penicillin and aureomycin	Saline	5	Walls moderately clean; size 3 by 1 cm.	Plasmin and hyaluronidase	0	8	0	8	None	Clean granulations 24 hr.; drainage decreased rapidly
3, F, 27	Abscess of breast postpartum	Incision and drainage	Penicillin	Saline	5	Walls covered with exuberant dirty granulations; size 5½ by 1½ cm.	Plasmin and hyaluronidase	0	5	23	28	None	Clear drainage, clean granulations 24 hr.; reaction, enzyme stopped; drainage increased again
4, F, 39	Abscess of breast, spontaneous	Incision and drainage	None	None	0	Walls necrotic yellow lining; approximately 30 cc. of pus evacuated	Plasmin Plasmin and bacitracin Plasmin, hyaluronidase and bacitracin	½ b.i.d. 1 b.i.d. 3 b.i.d.	0	?30	?34	None	Plasmin pack inserted in O.R.; volume: 1st postoperative day 10 cc., 3rd postoperative day 4 cc.
5, F, 30	Abscess of breast, spontaneous	Incision and drainage	Penicillin	Saline	8	Walls moderately clean; size 3½ by 1 cm.	None	0	0	16	18	None	Control case; curettage necessary because of excess granulations
6, F, 17	Abscess of breast postpartum	Incision and drainage	Penicillin	Saline	4	Size 2 by 4 cm.	None	0	0	25	25	None	Control case; drainage decreased rapidly
7, F, 26	Abscess of breast postpartum	Incision and drainage	Penicillin	Saline	6	Walls, dirty granulations; size 3 by 5 cm.	None	0	0	29	33	None	Control case; continuous foul drainage 10 days

* Duration of treatments is expressed in days unless otherwise specified.

† Frequency of treatments in the hospital or outpatient department (O.P.D.) is daily unless otherwise specified.

Note: Patients 1 and 2 were ideally treated with continuous plasmin and hyaluronidase and wounds closed in 9.5 days (average) compared to 25.3 days (average) in the saline-treated group (Cases 5, 6 and 7). Cases 3 and 4 were excluded from the enzyme-treated group because in Case 3 it was necessary to discontinue treatment with enzymes and, therefore, this was essentially a saline-treated case; in Case 4, since treatment was not continued by us after the patient left the hospital on the fourth day, the frequency of saline treatments and the total number of days until healing occurred are uncertain.

because of a general reaction which might have been due to the enzymes or to previously used antibiotics. After discontinuation of the treatment, drainage again increased and the wound took as long to heal as that of the controls.

The seventh patient in this group (Case 4) was treated with immediate instillation of plasmin and packing at the time of incision and drainage. When the pack was removed twenty-four hours later, the walls of the cavity were clean and without debris, and were covered with red granulation tissue. This is in contrast to the usual abscess cavity where the time necessary for red granulations to replace yellow fat or debris completely varies from a few days to several weeks. In the next forty-eight hours the volume of the cavity decreased from 10 to 4 cc. (a decrease of more than one-half) and the patient was ready for discharge from the hospital. Unfortunately, the patient was lost from our control and was treated irregularly with a saline solution after discharge. The healing time of the wound is not exactly known but was approximately thirty days (the same healing time as in the control patients).

11. *Open Infected Wounds* (*Table II*). Fifteen open granulating wounds of the abdomen, thigh and back which previously had been treated with Dakin's solution or saline and antibiotics for varying but usually prolonged periods were treated as described. Within twenty-four hours after the beginning of treatment with enzymes most of these wounds were free of gross purulent material and debris, and within forty-eight hours healthy granulation tissue was present. The time for complete débridement of slough varied from one to twenty-one days, with 75 per cent of the wounds being clean in seven days or less. In those cases in which the treatment was begun as an initial dressing or within the first twenty-four hours, the results were even more satisfactory.

Case 19 demonstrates this result well. This patient had a large infected wound following the insertion of a pin for a fractured hip. Twelve hours after the evacuation plasmin-saturated gauze was packed loosely into the wound, which contained pus and debris after removal of the initial saline pack. Twelve hours later, when the plasmin pack was removed, no pus or debris was present; thirty-six hours later the walls were completely covered with pink granulations. Hyaluronidase and terramycin were then administered. In two weeks the volume of the wound was reduced to one-half and the patient was discharged to the outpatient department. There was no evidence of toxic absorption in this patient in whom enzymes had been instilled into a relatively fresh wound. It was believed that complete débridement was accomplished much more rapidly in this case because of early use of enzymes.

In cases of longer duration, in which fibrosis had occurred before treatment was started or in which chronic infection was established, the time of cleansing and healing was lengthened; nevertheless, excellent results were obtained, as in Case 13. This patient, an obese (264 pound) diabetic woman, was admitted to the hospital because of a myocardial infarction. Panniculitis developed while she was being treated for the heart lesion. Infection persisted and the skin of the abdominal wall became black and non-viable approximately two months after admission. The wound was excised at this time and the subcutaneous abscess was found to contain a moderate amount of foul-smelling, seropurulent material. The base and walls were covered with a shaggy, tan exudate. Treatment was started with penicillin three times a day and streptomycin twice a day systemically, and neomycin ointment four times a day locally. The streptomycin was continued for one week and the neomycin ointment, preceded by saline irrigation, was continued for three days. Trypsin was used for one day. Sharp débridement was performed daily for the next month; the saline irrigations were replaced by Dakin's solution after the third day, at which time the neomycin ointment was discontinued. Despite this active treatment, approximately one month after the original excision progress notes on the patient's chart read, "Dakin's not accomplishing much." The walls of the wound were still covered with shaggy debris.

Daily treatment with plasmin instillations and packs was begun at this time, and the wound volume was measured as 50 cc. Within one week "much of the necrotic base was replaced with red granulations" and the wound was markedly improved. In fifteen days the volume was less than 40 cc.; all the walls were pink and granulating and the patient was ready for discharge. One week later, three weeks after the onset of plasminogen therapy,

TABLE II
OPEN INFECTED WOUNDS

Case No., Sex and Age (yr.)	Type of Wound and Etiology	Previous Therapy			Duration* of Local Previous Therapy	Condition and Size of Wound at Onset of Enzyme Therapy	Local Treatment. Agent, Duration* and Frequency†				Total No. of Days until Healed	Concomitant Systemic Therapy: Drug and Duration*	Comments
							Enzymes			Saline Only			
		Procedures	Systemic	Local			Drugs	In Hospital	In O.P.D.	In O.P.D.			
8, M, 60	Granulating abdominal wound secondary to wound infection	Incision and drainage	Penicillin	Saline	17	Walls, gray slough and necrotic debris; size 7.5 by 2.5 cm.; volume 20 cc.	Plasmin	7 b.i.d. 2 q.d.	7 q.2.d.	30	46	Penicillin, 4	Volumes: 2 days 10 cc., 7 days 5 cc., 9 days clean, no drainage
9, M, 50	Granulating abdominal wound secondary to subcutaneous abscess	Incision and drainage	Penicillin and terramycin	Saline packs	4	Walls, shaggy yellow debris; size 6 by 3 by 3 cm.	Plasmin and terramycin	5		0	42	Penicillin and terramycin, 6	Four days wound clean without drainage; 5 days O.P.D.
10, M, 35	Granulating abdominal wound secondary to subcutaneous abscess	Incision and drainage	Penicillin and dihydrostreptomycin	Saline packs	2	Walls, yellow debris; volume 30 cc.	Plasmin Plasmin	3	35, 3 × wk. 14 q.d. 7 q.2.d. 21 weekly	75	123	Penicillin and dihydrostreptomycin, 3	Three days wound clean; patient continued to work while being treated in O.P.D.
11, M, 44	Granulating abdominal wound secondary to subcutaneous abscess	Incision and drainage	Neomycin, aureomycin	None	0	Walls, yellow debris; volume 80-90 cc., pus evacuated; size 7 by 6 by 4 cm. irregular	Plasmin	7 b.i.d.	0	0	Lost to follow-up	Penicillin and dihydrostreptomycin, 5	Two days wound completely clean; 7 days volume 3 cc.
12, F, 55	Granulating abdominal wound secondary to necrosis of skin flaps	Radical vaginectomy, vulvectomy and groin dissection for carcinoma of the cervix	Penicillin, streptomycin, terramycin	SK-SD	40	Walls, grayish cast and some yellow debris	Plasmin Saline	14 b.i.d. 14 t.i.d.	0	0	Grafted	Terramycin, erythromycin, chloromycitin, furadantin	Fourteen days all debris cleaned; walls covered with red granulations; successful split-thickness graft
13, F, 57	Granulating abdominal wound secondary to panniculitis in an obese diabetic patient	Excision of slough	Penicillin 4 wk. t.i.d.; streptomycin 7 days b.i.d.	Débridement 4 wk. q.d.; neomycin ointment 3 days q.i.d.; trypsin 1 day; saline and Dakin's solution 4 wk. t.i.d.	28	Walls covered with yellow exudate; volume 50 cc.; size 12 by 5 by 4 cm.	Plasmin	20	0	180	210	Penicillin, 21	Seven days much of necrotic base replaced by granulations; 15 days volume 40 cc., all clean and granulating
14, M, 72	Granulating abdominal wound secondary to wound infection	Incision and drainage	Penicillin 1 day t.i.d.; streptomycin 1 day; terramycin 1 day	Saline irrigation and packs q. 6 hr.	3	Base yellow with shallow craters; volume 10 cc.; size 9 by 4 by 1 cm.	Plasmin and terramycin	7 b.i.d.	0		Patient died 3 weeks after discharge; no follow-up	None	Four days size 1 by 2 cm., base red, craters filled in; 7 days, clean and pink
15, F, 70	Granulating abdominal wound secondary to wound infection	Incision and drainage	Penicillin	Saline	2	Walls, yellow necrotic exudate; volume 17 cc.	Plasmin and terramycin	30	7	165	195	Penicillin, 28; streptomycin, 6; terramycin, 14	Wound thoroughly cleaned in a few days; patient in hospital be-

							varidase						cause of underlying disease; wounds kept open as sinuses by discharging silk
16, M, 47	Granulating abdominal wound secondary to wound infection	Incision and drainage; removal of silk	Penicillin	Saline	18	Walls moderately clean; size 5 by 16 cm.	Plasmin and hyaluronidase	0	30	5	35	None	None
17, M, 30	Granulating abdominal wound	Wide excision	Penicillin	Saline	14	Walls clean, granulating; size 3 by 6 cm.	Plasmin and hyaluronidase	0	11	0	12	None	None
18, F, 73	Granulating thigh wound secondary to wound infection	Incision and drainage	Penicillin	Saline t.i.d.	1	Walls very dirty with yellow lining; volume 30 cc.; size 10 by 6 cm.	Plasmin and terramycin	5	0	45 q.2.d.	60	Penicillin and terramycin, 6; terramycin, 5	Volumes: 6 days 18 cc., 13 days completely clean, 16 days 5 cc.
							Plasmin, hyaluronidase and terramycin	8					
19, M, 43	Granulating thigh wound secondary to wound infection	Incision and drainage	Penicillin and streptomycin 5 days; penicillin 7 days	Saline pack 12 hr.	½	Walls full of pus and debris; volume 5 cc.; size 6 by 2 cm. with long sinus tract	Plasmin	3 b.i.d.	10	21	46	Penicillin and terramycin, 15	Twelve hr. no pus, very little debris; 48 hr. no debris, good granulations throughout 2 wk.; volume reduced to 2 cc.
							Hyaluronidase and terramycin	5 b.i.d.					
							Hyaluronidase and terramycin alt. with saline q.d.	7 q.d.					
20, F, 41	Granulating thigh wound secondary to infected hematoma	Incision and drainage	Erythromycin	Saline packs	5	Walls yellow-red with much shaggy, loose debris and a 4 cm. sinus tract; volume 8–10 cc.; size 10 by 4 by 6 cm.	Plasmin and bacitracin	9 b.i.d. 4 q.d.	0	0	?	Erythromycin	Six days all pink granulations, no debris; 10 days volume 5 cc.; 24 days volume 2 cc.; patient was a malingerer and kept wound open
21, F, 53	Open amputation stump	Breakdown of mid-thigh amputation for gas bacillus	Terramycin, gantrisin	Dakin's solution	7	Walls, creamy, shaggy debris on walls and muscles; 8 cm. of femur exposed; volume 350 cc.	Plasmin and bacitracin	35	Patient taken to O.R. for removal of protruding femur and revision of stump			Gantrisin	Seven days 90% purulent exudate gone; 21 days entire wound clean, exposed femur completely covered with granulation, volume 175 cc.
22, F, 59	Granulating wound of the right scapular area	Burn	None	Ointment at home 3 wk.; saline packs in O.P.D. and hospital 7 days	28	Punched-out cavity, 1¼ by ½ by ¼ inches, containing thick yellow-green purulent exudate; volume 1½ cc.; surrounding area of granulations with some yellow debris, 4½ by 3 inches	Plasmin and bacitracin	7 b.i.d.	0	Currently being treated with saline in O.P.D.		None	Five days 90% thick exudate gone, base pink granulations; 7 days enzymes stopped, split-thickness grafts applied to area around punched-out cavity, 100% take

* Duration of treatments is expressed in days unless otherwise specified.

† Frequency of treatments in the hospital or outpatient department (O.P.D.) is daily unless otherwise specified.

Note: The majority of these cases did not receive the ideal treatment of continuous enzymatic applications and took a proportionately longer period to close than Cases 16 and 17 in which treatment was with enzymes until the wound was completely closed. On the other hand, using enzymes initially only was of definite advantage in cleaning wounds more rapidly than a saline solution or Dakin's solution as pointed out in the text, which permitted earlier discharge of the patient to the O.P.D.

she was discharged. Arrangements were made for outpatient visits by the Visiting Nurse Association for daily saline irrigations. This case illustrates the rapid débriding effect of plasminogen where conventional therapy had failed to show any progress in four weeks.

Many of the wounds in this group of patients were rapidly brought to the stage of débridement where grafting could easily be undertaken, and in the future grafting will undoubtedly be done much earlier. Case 12 was such a case, and in Case 21 an early revision of an infected amputation stump was possible.

Patient 12 had a large, dirty, granulating abdominal wound secondary to sloughing of the skin flaps from radical pelvic surgery for carcinoma of the cervix. She had been treated with streptokinase-streptodornase locally, and penicillin, streptomycin, terramycin and chloromycetin® systemically for forty days. Despite this the walls of the wound had a grayish cast and there was yellow debris along the walls. Progress appeared arrested and the wound was not clean enough for a secondary procedure. Plasmin was instilled twice a day, and within two weeks the walls were a healthy red and ready for a split-thickness graft. This was successfully applied and a complete take resulted.

Unfortunately, only three patients in this group were treated ideally with both plasmin and hyaluronidase (Cases 16, 17 and 19); only one other patient was treated with plasmin alone until the wound healed completely (Case 9). The wounds treated with both plasmin and hyaluronidase healed more rapidly than those wounds in which plasmin alone or plasmin and antibiotics were used until the debris had been cleared.

The majority, if not all, of these patients were discharged to the outpatient department earlier than could have been expected if routine methods had been used. This represents a great saving in expense, hospital space and patient rehabilitation. Since it was not feasible to follow up many of these patients after discharge, the care of the wounds was completed with saline alone rather than with hyaluronidase. Even in those cases in which the ideal treatment was not continued with hyaluronidase until the wound had healed completely, it was found that after the wounds were completely débrided with plasmin, they could be kept clean on saline irrigations in the outpatient department; however, healing took longer than it would have with continued treatment. These cases acted as controls for similar-sized wounds such as those previously mentioned which received the ideal treatment. In a comparison of similar granulating wounds where hyaluronidase was not used (Cases 8, 10, 13 and 15) with cases in which hyaluronidase was used until complete healing was achieved (Cases 16 and 17) it is evident that the latter healed more rapidly.

III. *Sinus Tracts* (*Table III*). Sinus tracts leading to large cavities (Cases 23 to 25): The results in these cases and in those of small sinus tracts discussed in the following category are perhaps the most striking of any of the cases treated. We believe that in this type of case enzyme treatment will be of the greatest value to the patient and the physician. Three patients with narrow sinuses leading to large cavities of various types were treated, all with complete healing in relatively short periods of time without any further surgical treatment.

Case 24 was an eighteen month old female baby who had been operated upon for excision of a large sacral lipoma. This procedure left a presacral dead space. The wound continued to drain but narrowed down to a small sinus opening after two weeks. At this time it was suggested that the patient be treated with enzymes; however, the physician in charge refused this therapy because of fear of a pyrogenic reaction, and the usual methods of treatment were continued. The wound seemed to heal superficially after forty days and the patient was discharged, but a few days later the sinus tract again opened and began to drain actively. Examination at this time revealed a healed, transverse, lower sacral wound with a sinus opening from which a cloudy, purulent fluid drained. With careful probing the sinus was found to enter a large undermined area, 12 by 16 cm., overlying the sacrum. Cultures showed no growth. Treatment was begun with plasmin instillations for twenty minutes each day, followed by insertion of a wick soaked in hyaluronidase. On the second day after treatment was started drainage from the wound was entirely clear and the sinus edges were clean. After fifteen days of treatment the cavity was obliterated, the sinus closed and it has remained well healed for two and a half years.

Another patient (Case 23) had a large retro-

TABLE III
SINUS TRACTS

Case No., Sex and Age	Type of Wound and Etiology	Previous Therapy			Duration of Local Previous Therapy*	Condition and Size of Wound at Onset of Enzyme Therapy	Local Treatment: Agent, Duration and Frequency†				Total No. of Days until Healed	Duration of Concommitant Systemic Therapy*	Comments
							Enzymes			Saline Only			
		Procedures	Systemic	Local			Drugs	In Hospital	In O.P.D.	In O.P.D.			
23, M, 42	Right retroperitoneal sinus tract secondary to regional ileitis	Incision and drainage of retroperitoneal abscess	Penicillin and streptomycin	Saline	2	Walls, yellow exudate; volume 75 cc., pus obtained	Plasmin and bacitracin	9 b.i.d.	0	70	84	9	Four days exposed sinus lined with red granulations; 5 days volume 25 cc.; saline irrigations in O.P.D.
24, F, 18 mo.	Large fluid collection in an undermined sacral wound with narrow sinus	Spontaneous rupture	Penicillin and streptomycin	Saline	47	Walls dirty, narrow sinus; size 12 by 16 cm.	Plasmin and hyaluronidase	0	15	0	15	None	Two days no purulent material; rapid obliteration
25, M, 52	Perineal sinus tract with large cavity secondary to abdominoperineal resection	Large wound left open at operation	Penicillin, streptomycin, aureomycin	Saline; curettage	228	Walls, very dirty granulations with foul drainage; size 2 by 15 cm.	Plasmin, hyaluronidase and terramycin	0	30	5	35	None	Seventy-two hr. clean, drainage almost absent
26, M, 46	Chronic sinus, upper abdominal wound	Sinus tract from silk sutures	Penicillin	Curettage; removal of silk; saline	34	Walls, moderately purulent drainage; size ½ by 5 cm.	Plasmin and hyaluronidase	0	10	0	12	None	One day clean serous drainage; 5 days silk suture extruded
27, M, 50	Chronic sinus, subcostal gallbladder wound	Incision and drainage of wound infection	Penicillin	Curettage; saline packs	20	Walls clean, drainage minimal; size 5 by 2 cm.	Plasmin and hyaluronidase	0	15	0	15	None	Rapid healing from base
28, F, 62	Sinus gastrectomy wound	Sinus tract from silk sutures	Penicillin, streptomycin	Removal of silk; saline	37	Walls, dirty granulations; size 3 by 10 cm.	Plasmin and hyaluronidase	0	30	0	30	None	Two days purulent drainage ceased, little serous drainage
29, M, 24	Sinus appendectomy wound	Incision and drainage of wound infection	Penicillin	Curettage; saline wicks	10	Walls moderately clean; size 3 by ½ cm.	Plasmin and hyaluronidase	0	7	0	7	None	Rapid cleaning and closure
30, M, 53	Sinus gallbladder wound	Incision and drainage of wound infection	Penicillin	Curettage; saline wicks	22	Size 6 by 1½ cm.	Plasmin and hyaluronidase	0	14	0	15	None	Twenty-four hr. wound clean
31, F, 24	Sinus in perineum secondary to abdominoperineal resection	Large cavity left open at operation	Penicillin	Curettage; saline	47	Walls, very dirty granulations; size 1 by 10 cm.	Plasmin, hyaluronidase and terramycin	0	21	0	21	None	Forty-eight hr. wound clean, rapid healing

* Duration of treatments is expressed in days unless otherwise specified.

† Frequency of treatments in the hospital or outpatient department (O.P.D.) is daily unless otherwise specified.

Note: Patients 24 to 31 were treated as outpatients with excellent results. All wounds healed completely with fewer days of treatment than with the previous unsuccessful therapy. In general, the older the sinus when treatment was started, the longer treatment was necessary for healing. Patient 23 had only plasmin with antibiotics for nine days; and although the wound was débrided quickly, it failed to heal as rapidly as those treated ideally, although it was fresher.

FIG. 1. Case 23. One week after treatment with plasminogen; note cavity fills out better and appears to be smoother and larger due to lysis of debris.

FIG. 2. Same case. Three weeks after onset of plasminogen therapy showing cavity much reduced in size. At the time this x-ray was taken the patient was being treated with a saline solution in the outpatient department.

peritoneal abscess in the right flank secondary to regional ileitis. A small drainage incision was made and the cavity was estimated to contain 75 cc. of pus. The visualized portion of the cavity had dirty yellow walls. The sinus was narrow and had a long retroperitoneal course. Adequate drainage of this cavity would obviously have necessitated extensive surgical incisions and would still not have insured against pocketing or recurrent abscess formation. Lipiodol study showed a large irregular cavity. Enzyme treatment was started. One week afterward the cavity appeared larger, as is common, due to the fact that the debris had been lysed and the walls of the cavity were smoothed. (Fig. 1.) It was also noted that the wound was clean, that it was lined with pink granulations and that the dye used for visualization of the cavity flowed in more readily and the cavity filled more easily without discomfort to the patient. After one week the measured volume of the cavity was 25 cc. Two days later there was no drainage and the patient was discharged to the outpatient department and treated with saline only. Subsequent x-rays in the outpatient department showed continued decrease in the size of the cavity. (Fig. 2.) It should be noted that in this case ideal treatment with enzymes was not given continuously until the wound had closed completely.

In Case 25 the patient, a fifty-two year old white man, had had a deep draining perineal sinus tract for more than eight months following an abdominoperineal resection. When first seen by us the tract was 15 cm. in length and had a maximum diameter of 2 cm. The tract was filled with exuberant granulations. In this case the enzyme mixture was instilled through a catheter and within three days the wound was clean and only clear returns were obtained. The tract was kept open simply by the insertion of the catheter and the instillation of the enzyme. The wound was healed completely in thirty-five days.

Chronic simple sinus tracts (Cases 26 to 31): One persistent perineal sinus tract following abdominoperineal resection and five persistent sinus tracts following various abdominal procedures were treated with this method. Healing occurred in from seven to thirty days, with an average of approximately twelve to fifteen days.

It is of interest that all nine cases of sinus tracts healed completely. In those ideally treated (Cases 24 to 31) the longest healing time was thirty-five days. It is also significant that all ideally treated sinuses healed in a shorter time than had elapsed during previous

unsuccessful treatment. Again it was noted that in general, the older wounds healed more slowly than those of shorter duration. Six of the nine patients in this group (Cases 23 to 31) were treated without antibiotics, making it evident that the enzymes alone were responsible for the cleansing of the sinuses.

COMPLICATIONS

No complications were proved to be due to the enzymes themselves. In one patient (Case 3, Table 1) a mild serum-type reaction developed with periorbital edema, dermatitis and slight swelling of the ankles five days after the beginning of local treatment with instillations of plasmin and hyaluronidase. An elevated eosinophil count was present. The patient responded to conservative measures and the administration of pyribenzamine.® After forty-eight hours no further difficulties were encountered. It is conceivable that this reaction was due to antibiotics used previously in this case. No other reactions were observed even in those patients in whom the enzymes were used immediately after opening the abscess (Case 4, Table 1) or within twelve hours afterward (Case 19, Table 11).

COMMENTS

Previous studies have shown the effectiveness of enzymatic débridement with SK-SD, trypsin and bovine plasmin. There are, however, certain disadvantages to the first two materials, especially SK-SD, since they are likely to produce pyrogenic reactions especially if injected into closed cavities or even into large open wounds. With both trypsin and SK-SD, inhibitors are developed in the patient after a period of ten days to two weeks, and as a result their activity may be significantly decreased or lost. Trypsin, a proteolytic enzyme in itself, is very active in digesting necrotic debris and fibrin but has other disadvantages. These include the short duration of its activity with very rapid loss of activity after two hours, and the fact that it tends to digest all proteins and may in certain instances, as have been reported, digest partially viable tissue. A more common difficulty with trypsin is its irritating effect which has led some patients to refuse further treatment. The development of inhibitors to trypsin, so-called antiproteolytic materials or antitrypsin, necessitates progressive increases in the amount of the drug used.

Since human plasminogen was available for study and since it was known that the function of streptokinase is the activation of this material to plasmin (fibrinolysin), it seemed logical to proceed with this study of the effect of plasmin itself in the débridement of wounds. It should be stressed that although streptokinase (varidase) was used to activate plasminogen, the quantities used were insufficient to produce the effect themselves, especially since *in vitro* tests showed almost no excess of streptokinase present after activation (0.5 cc. SK-SD to 10 cc. plasminogen).

Theoretically, by removing slough and debris from a wound and from its walls with plasminogen, the barriers to antibiotics administered locally or systemically would be broken down and the antibiotics could penetrate the infected areas better. Although this theory may be true, there is no definite evidence in our series to prove that there was any material improvement in the cleaning or healing of the wounds where antibiotics were used as compared with those cases in which enzymes alone were used. It might also be feared that infection would be spread by the use of these enzymes, but again there is no objective evidence that this occurred. At present a well controlled study is being made of these problems using fresh abscesses and taking bacterial colony counts. In our cases the remarkable rapidity with which the fibrin clots and necrotic debris were removed from the wounds and the rapidity with which the chronically infected granulation tissue became clean and healthy looking was most impressive. Almost without exception the drainage became clear and lost its foul odor within twenty-four to forty-eight hours after treatment was begun. Wounds with copious drainage showed obvious diminution in the amount of drainage very quickly.

It is possible that the improvement of the infection in these wounds is the purely mechanical effect of the removal of a good culture medium from the cavity. Another possibility is that by improving diffusion into the abscess wall the defensive mechanisms of the body are permitted to act on and destroy the organisms.

Regardless of the mechanism of action, it is apparent that wounds were at least improved sufficiently so that either the patient could be discharged to outpatient care or the wound could be closed secondarily or grafted far more quickly than with the usual treatments, with

or without antibiotics. This results in a significant saving in hospital time and expense.

With plasminogen the following advantages were gained over other types of enzymatic treatment of wounds: (1) A known amount of fibrinolytic enzyme was supplied independent of the local natural supply in the exudates of the wound. This supply permitted control over the activity of the enzyme. (2) No definite allergic reactions were found. (3) There were no pyrogenic reactions. (4) No definite evidence of active inhibiting substances in the wounds was observed. (5) No pain was experienced by the patient.

There is no reason to expect that plasmin would have any direct effect on the healing of wounds other than by removing debris and pus as does SK-SD or trypsin. Another material was then sought to increase healing, to be used in conjunction with or after the débridement. Hyaluronidase was considered for this purpose. There were two theoretic considerations for the use of hyaluronidase, based on its effect on the ground substance: (1) Hyaluronidase would reduce the tissue tension associated with edema, permit better diffusion of nutrient materials and allow more rapid growth of capillaries into the walls of abscess cavities and thus produce more rapid healing. (2) By the same effect, hyaluronidase would permit diffusion of antibiotics given systemically or applied locally to the surrounding tissue.

The results would seem to support these theoretic considerations, for in the wounds where hyaluronidase was added healing was apparently markedly hastened as compared with wounds treated with saline, with antibiotics alone, or with plasmin alone continued for a longer period.

Obviously the results of this study are not of statistical significance but we believe a review of Tables I to III will support our opinion that the results are encouraging. Further investigation is warranted to evaluate the effect of hyaluronidase on wound healing.

SUMMARY

Treatment of chronic surgical wounds and sinuses with a combination of plasmin and hyaluronidase is presented with the rationale for the use of these agents. The results show hastening of cleansing of the wound and healing, which is very gratifying as compared with other methods of treatment. The method was simple, the treatment safe. Earlier discharge of patients from the hospital and earlier closure of these chronically infected wounds were effected.

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Intrathecal Inoculation of Mouse Sarcoma 180 and 37 in the Cat and Dog

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SARCOMA 180 and 37 are native mouse tumors. This report deals with observations made when these tumors were inoculated into the cisterna magna of the cat and dog. Cerebrospinal fluid withdrawn from the cisterna magna at intervals following such single and multiple transitory heteroinoculations was injected subcutaneously into normal mice in an attempt to grow tumors.

DESCRIPTION OF EXPERIMENTS*

Suspensions of tumor cells in normal saline were prepared by cutting up and macerating under sterile precautions (with a mortar and pestle) portions of sarcoma 180 tumors from Longacre mice and portions of sarcoma 37 tumors from Paris RIII mice. The suspensions were injected into the cisterna magna of adult cats. The suspensions contained viable, dead and dying tumor cells, as well as all the other constituents of the tumor. Usually an amount of cerebrospinal fluid was withdrawn equal to the volume of suspension to be injected. The cisternal taps and intraspinal injections were done under sterile precautions and under general ether anesthesia.

The cats stood the procedure surprisingly well. In several of them purulent conjunctivitis and nasopharyngitis developed after a few days, and persisted in some instances for a few weeks. When the cerebrospinal fluid of a cat with such a condition was transferred into the cisterna magna of a normal cat, the same type of conjunctivitis and nasopharyngitis was induced. Some infectious element, transferable by intraspinal injection and existing in the tumor, appeared likely.

* The first intracisternal inoculations of mouse sarcoma 180 were given to cats Nos. 215 and 216 on January 24, 1942.

TABLE 1
RECOVERY OF MOUSE SARCOMA 180 TUMORS AFTER A SINGLE TRANSITORY HETEROINOCULATION INTO THE CISTERNA MAGNA OF CATS

No. of Days	Cat	Cerebrospinal Fluid of Cat Injected into Normal Mice (cc.)	Tumor Takes	No Takes
1	251	0.5, 0.5, 1.0	..	3
	297	0.1, 0.2, 0.2	..	3
2	251	0.5, 0.5, 0.5	2	1
	284	0.1, 0.1	1	1
	282	0.25, 0.25	1	1
		0.5	1	..
3	251	0.5, 0.5	..	2
		1.0	..	1
4	251	0.5	1	..
		0.7, 0.8	..	2
5	285	0.2, 0.5, 0.5	..	3
7	286,288	0.1, 0.1	..	2
	290,292	0.2, 0.2	..	2
	251	0.3, 0.5, 1.0	..	3
	291	0.4	..	1
	287,289	0.5, 0.5	..	2
	293,296	0.5, 0.5	..	2
	294	0.7	..	1
11	215	0.25, 0.5	..	2
	251	0.5, 0.5, 0.5	1	2
12	215	0.05, 0.05	..	2
		0.1(6)	..	6
		0.2, 0.2, 0.2	..	3
		0.5	..	1
	216	0.1, 0.1, 0.5	..	3
40	215	0.4, 0.4, 1.5	..	3
115	216	0.5, 1.0, 1.0	..	3

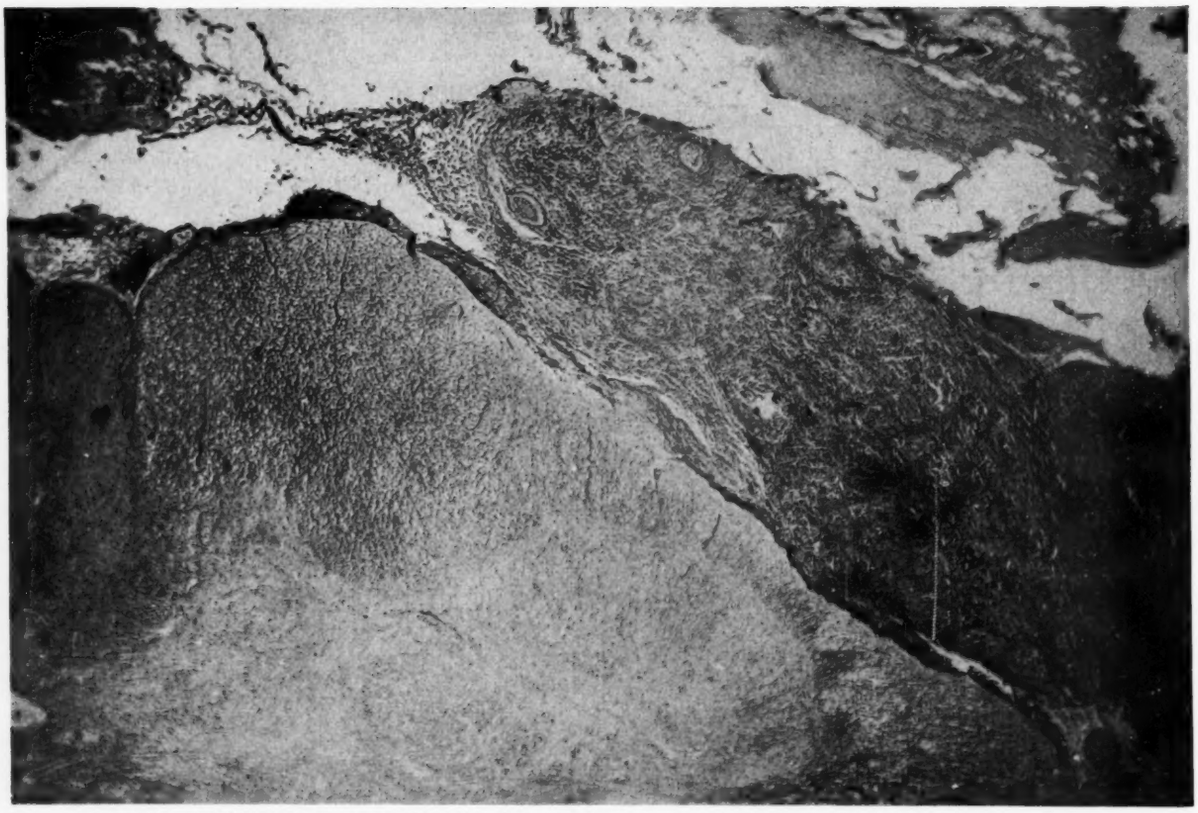

FIG. 1. Cat 286, serial No. 58426. Animal received four cisterna magna injections of suspensions of mouse sarcoma 180 at intervals of one week; sacrificed two days after last inoculation. Cervical cord showing thickening of meninges and obliteration of subarachnoid space, dorsal area. Hematoxylin and eosin, original magnification × 38.

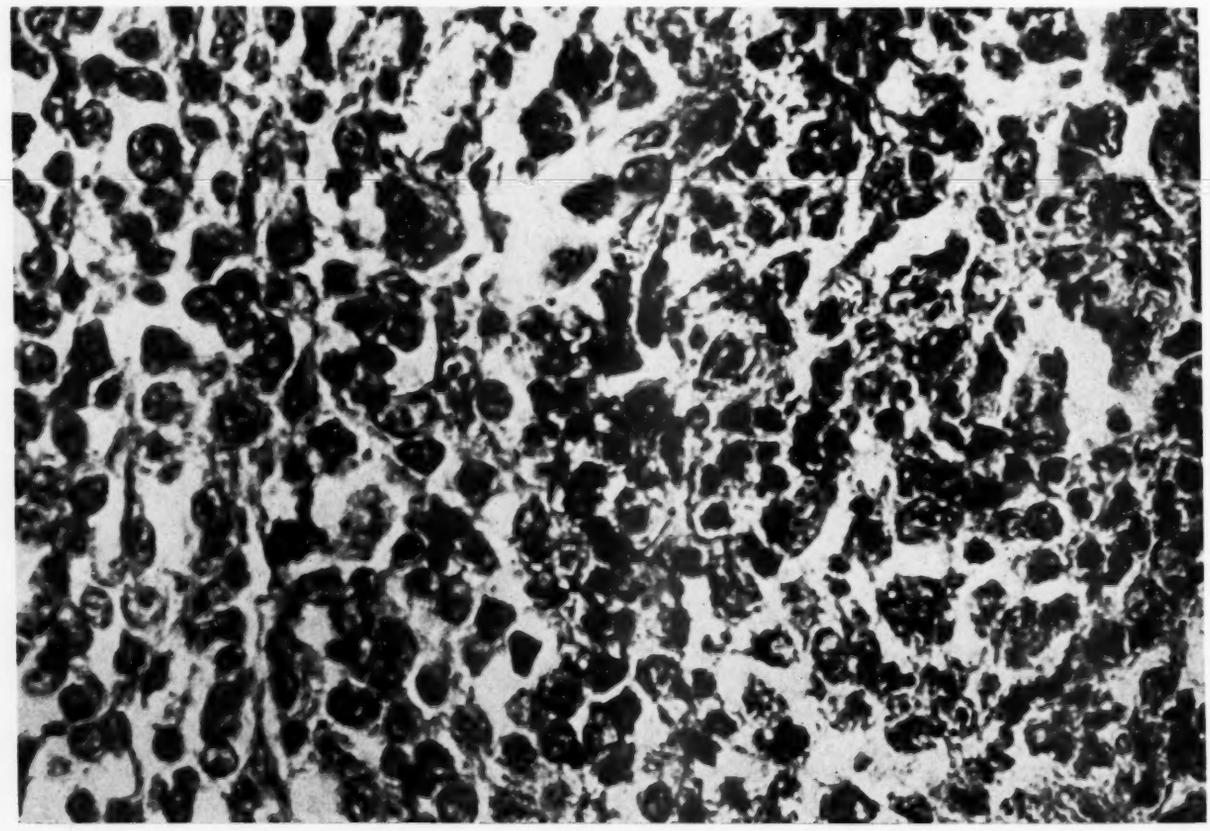

FIG. 2. Same cat as Figure 1. Productive reaction of arachnoid membrane to sarcoma 180 tumor cells. Hematoxylin and eosin, original magnification × 880.

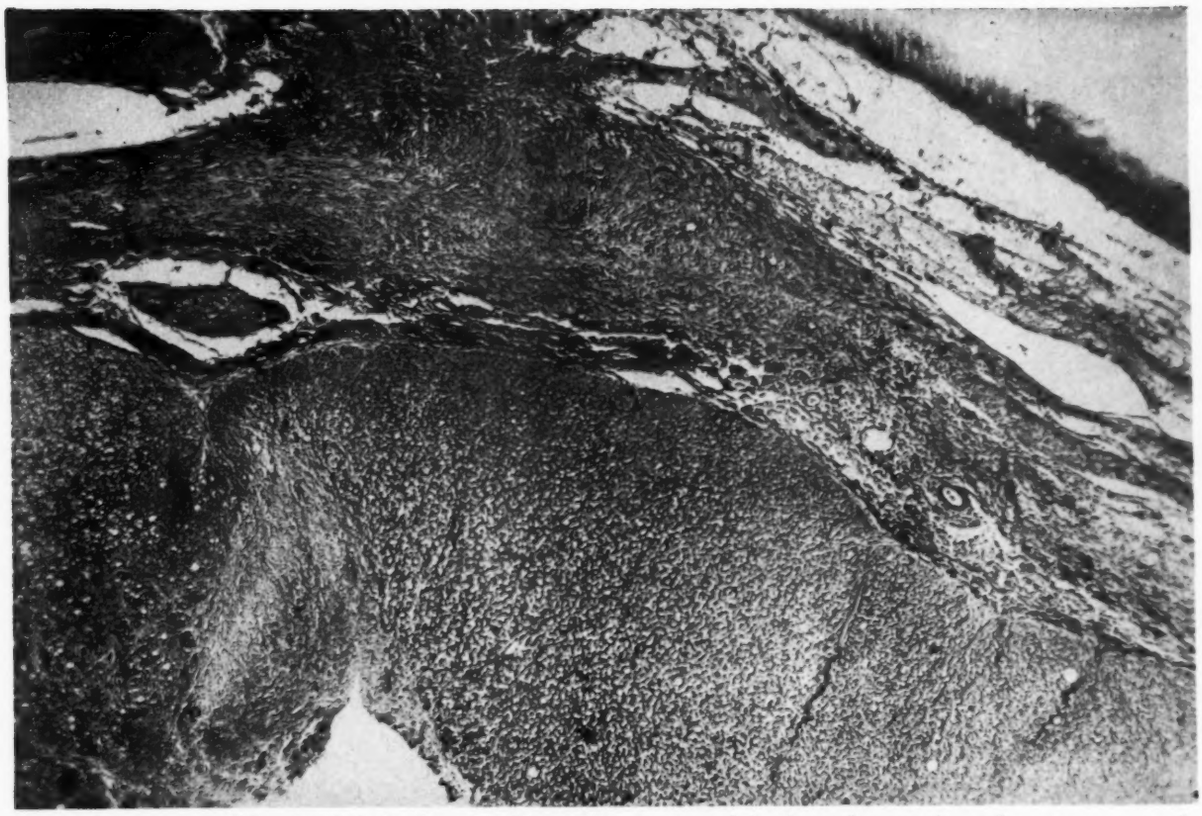

FIG. 3. Cat 293, serial No. 58456. Animal received four cisterna magna injections of suspensions of mouse sarcoma 180 at intervals of one week; sacrificed nine days after last inoculation. Lower region of medulla, showing same type of productive thickening of meninges as in Figure 1. Hematoxylin and eosin, original magnification × 38.

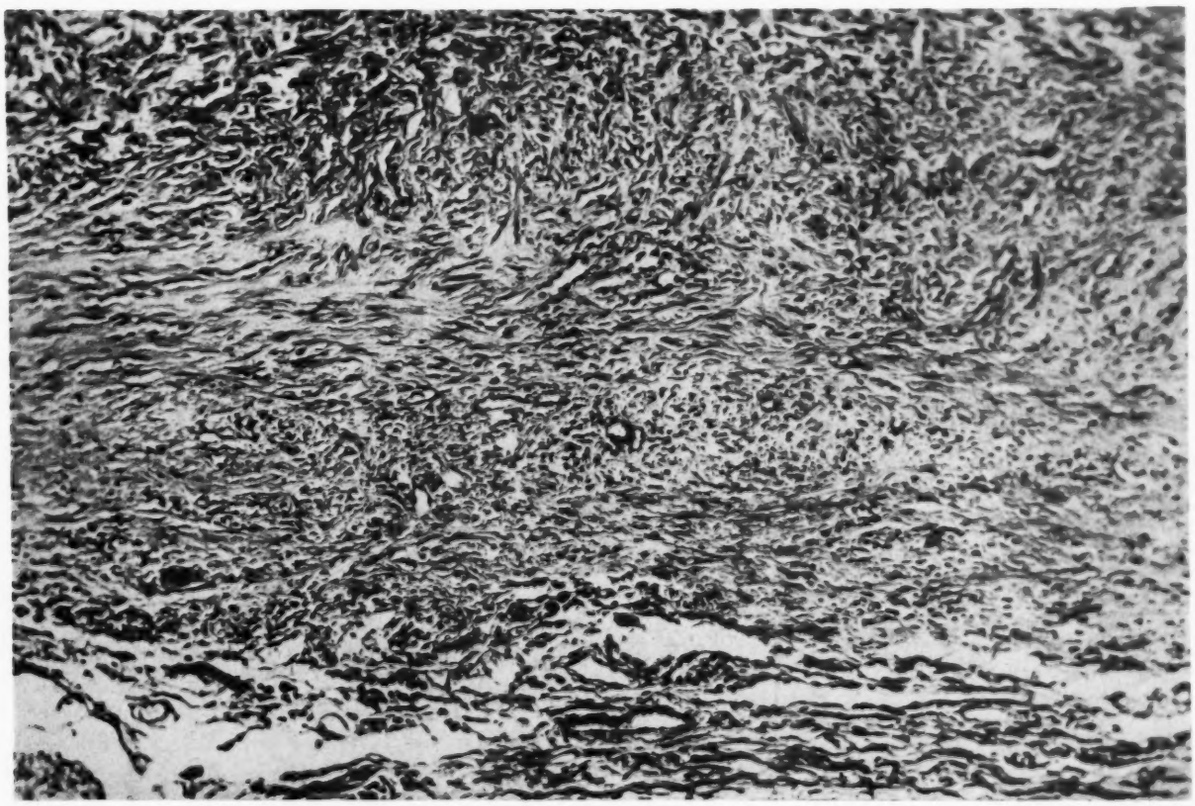

FIG. 4. Same cat as Figure 3. Productive reaction in subarachnoid space to sarcoma 180 tumor cells. Hematoxylin and eosin, original magnification × 73.

TABLE II

RECOVERY OF MOUSE SARCOMA 180 TUMORS AFTER MULTIPLE TRANSITORY HETEROINOCULATIONS INTO THE CISTERNA MAGNA OF CATS

Cat	No. of Days after Last Inoculation	No. of Inoculations	Interval (days)	Cerebrospinal Fluid of Cat Injected into Normal Mice (cc.)	Tumor Takes	No Takes
282	2	2	2	0.15 (2), 0.5		3
	2	3	2-2	0.4, 0.5 (2)		3
	7	4	2-2-2	0.4, 0.5 (2)		3
	2	5	2-2-2-7	0.2 (3)		3
	12	6	2-2-2-7-2	0.1, 0.5 (2)		3
251	4	2	11	0.3	1	
	2	3	11-4	0.3, 0.5		2
	2	4	11-4-2	0.5 (2)		2
291	7	2	7	0.1		1
286,287,288	..	..	.....	0.2 (8)		8
289,294	..	..	.....	.....		..
295,296	..	..	.....	.....		..
290	..	..	.....	0.3		1
293	..	..	.....	1.0		1
286	7	3	7-7	0.1		1
288	..	..	.....	0.2		1
293	..	..	.....	0.3		1
288,296	..	..	.....	0.4 (2)		2
286,289	..	..	.....	0.5 (3)		3
290	..	..	.....			
215	11	2	40	0.1		1
				0.2 (4)		4

TABLE III

RECOVERY OF MOUSE SARCOMA 37 TUMORS AFTER A SINGLE TRANSITORY HETEROINOCULATION INTO THE CISTERNA MAGNA OF A CAT (NO. 252)

Days	Cerebrospinal Fluid of Cat Injected into Normal Mice	Tumor Takes	No Takes
1	0.5	..	1
	1.0, 1.0	2	..
2	0.5	..	1
	1.0, 1.0	2	..
3	0.5, 0.5	..	2
	1.0	..	1
4	0.4, 0.6, 0.9	..	3
7	0.4	..	1
	0.5, 0.5	..	2
11	0.5, 0.5, 1.0	..	3

Several cats received repeated inoculations of tumor at intervals of a few days. Cerebrospinal fluid was removed after variable times following single and multiple inoculations. Smears were fixed in iodine vapor and stained for microscopic study. Subcutaneous injections were given to normal Longacre mice in an attempt to grow sarcoma 180 tumors, while normal Paris RIII mice were used to recover any sarcoma 37 tumors.

An adult brown setter was given 5 cc. of a suspension of mouse sarcoma 37 by injection into the cisterna magna. This injection was repeated in one week. Bloody diarrhea developed and the animal was prostrated for several days but then rallied and was able to take two additional inoculations of the same amount at intervals of thirteen and five days. Nine days after the last inoculation it was impossible to obtain any spinal fluid from the cisterna magna or from the lumbar region of the spinal canal.

TABLE IV

RECOVERY OF MOUSE SARCOMA 37 TUMORS AFTER MULTIPLE TRANSITORY HETEROINOCULATIONS INTO THE CISTERNA MAGNA OF A CAT (NO. 252)

Days after Last Inoculation	No. of Inoculations	Interval (days)	Cerebrospinal Fluid of Cat Injected into Normal Mice (cc.)	Tumor Takes	No Takes
4	2	11	0.5,* 1.0	..	1
2	3	11-4	0.5, 1.0†	1	..
2	4	11-4-2	0.4, 0.4	..	2

* Mouse died after 4 days.
† Mouse died after 1 day.

TABLE V

RECOVERY OF MOUSE SARCOMA 37 TUMORS AFTER TRANSITORY HETEROINOCULATION INTO THE CISTERNA MAGNA OF A DOG (NO. 1)

No. of Hetero-inoculations	Interval (days)	Days after Last Hetero-inoculation	Cerebrospinal Fluid of Dog Injected into Normal Mice (cc.)	Tumor Takes	No Takes
1	..	7	0.1	..	1
..	..	..	0.2, 0.2	2	..
2	7	13	0.2, 0.2, 0.2	..	3

A blockage of the subarachnoid space in the cervical region and medulla was found at autopsy.

Tables I to V give the essential details of these experiments.

OBSERVATIONS

After a single injection of a suspension of mouse sarcoma 180 into the cisterna magna of a cat, cerebrospinal fluid removed as late as eleven days after the inoculation grew a tumor when injected subcutaneously into a normal mouse. (Table I.)

Two days after single injections of sarcoma 180 into the cisterna magna, the cerebrospinal fluid of the cats grew tumors in normal mice in five of eight experiments (62.5 per cent) using three different cats. (Table I.)

When multiple injections of sarcoma 180 were given into the cisterna magna, as indicated in Table II, the cerebrospinal fluid of cats two days after the last injection failed to grow tumors in normal mice in thirteen experiments (100 per cent) using the cerebrospinal fluid from two cats. The cats appeared to have developed some type of resistance to the foreign tumor.

From a study of smears of cerebrospinal fluid withdrawn from the cats, and from the pathologic examinations of the spinal membranes of cats sacrificed at various times, the following sequence of events appeared to have taken place:

After an inoculation of the tumor suspension there was a flooding of the subarachnoid space with viable, dead and dying tumor cells and fluid. An immediate exudation of polymorphonuclear leukocytes was followed in twenty-four to forty-eight hours by that of round cells. Leukocytes were attracted to individual and clumped tumor cells. Large phagocytic cells were seen attached to single tumor cells. These phagocytic cells most likely came from the arachnoid membrane, which showed signs of proliferation and thickening. After a few days the cerebrospinal fluid withdrawn from the cisterna magna appeared watery clear and contained only a few round cells. No tumor cells were found in this fluid.

This reaction appeared accentuated when successive inoculations of tumor cells were given. After a number of inoculations the meninges appeared thickened, but in no case was there evidence that the tumor had "taken root."

Some of the pathologic reactions are shown in Figures 1 to 7.

COMMENTS

Foreign tumor cells of the type of sarcoma 180 and 37, when inoculated in the subarachnoid space in cats via injections into the cisterna magna, stimulated the arachnoid membrane to proliferate and to shed free phagocytic cells. This reaction is similar to that which has been reported following the subarachnoid injection of foreign red cells, carbon particles, India ink and cinnabar.[1] The arachnoid membrane may well be considered part of the reticuloendothelial system. It is believed that phagocytic cells of this system may produce globulin and that antibody globulin represents the synthesis of a new kind of protein from these cells under the influence of an antigen.[2]

In no other part of the body is there such an ideal anatomic arrangement where foreign tumor cells or antigens can be introduced into a cavity containing such reticuloendothelial tissue and a watery fluid normally containing no antibodies.

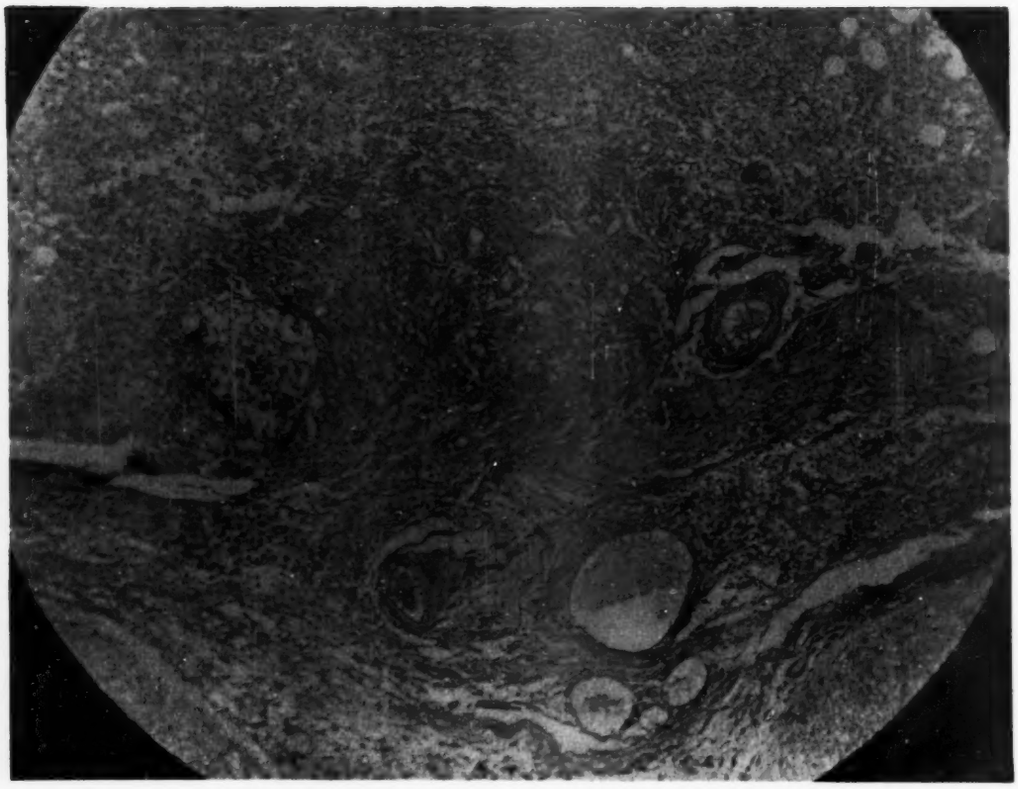

FIG. 5. Cat 288, serial No. 58427. Animal received three cisterna magna injections of suspensions of mouse sarcoma 180; sacrificed twenty-three days after the first injection, sixteen days after the second injection, nine days after the third. Upper cervical region spinal cord, showing similar productive reaction and formation of new capillaries in thickened membranes, region of dorsomedian sulcus. Hematoxylin and eosin, original magnification × 96.

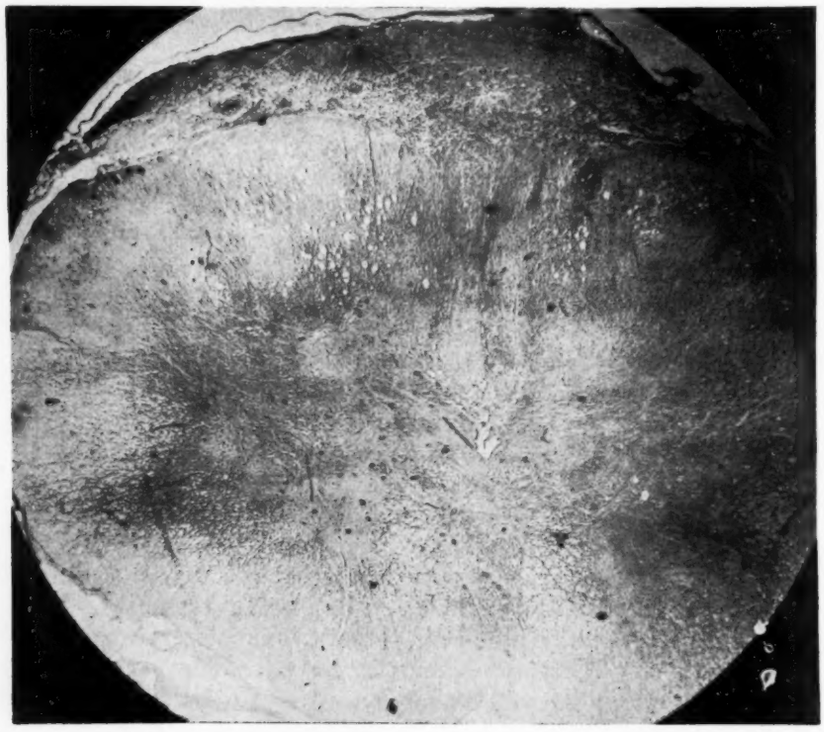

FIG. 6. Dog 1, serial No. 58523. Animal received four cisterna magna injections of suspensions of mouse sarcoma 37 at intervals of seven, thirteen and five days; sacrificed nine days after last inoculation. Upper cervical cord, showing proliferation, thickening and infiltration of meninges. Hematoxylin and eosin, original magnification × 19.

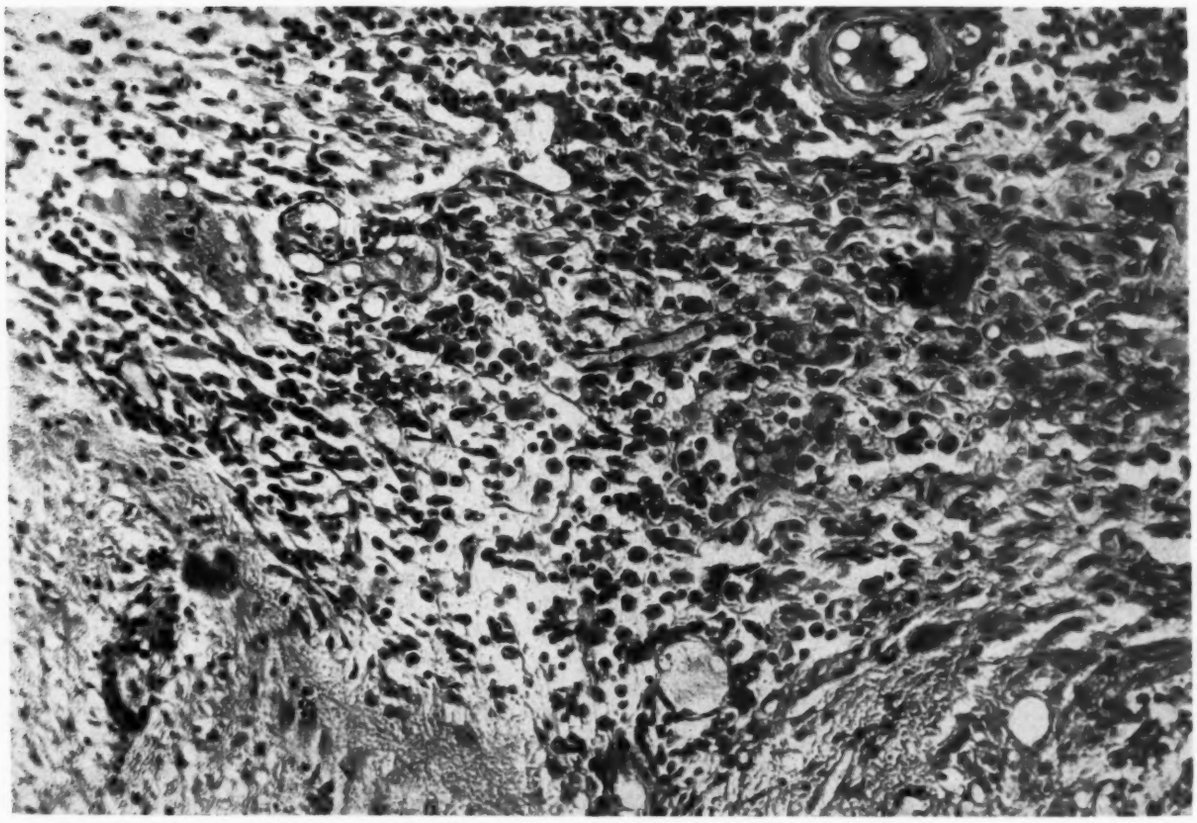

FIG. 7. Same dog as Figure 6. Productive reaction in subarachnoid space to sarcoma 37 tumor cells, region of dorsomedian sulcus. Shows similarity to the reaction to sarcoma 180 tumor cells in the cat, Figure 5. Hematoxylin and eosin, original magnification × 136.

Because of the small subarachnoid space and limited quantities of available cerebrospinal fluid in animals like the cat and dog, proliferation of the arachnoid membrane tends to block the subarachnoid space, making further inoculations of tumor and recovery of cerebrospinal fluid most difficult. It is hoped that by using large animals like the horse these experiments may be repeated in an attempt to recover specific tumor antibodies from the cerebrospinal fluid after such intraspinal immunization.

SUMMARY

1. Mouse sarcoma 180 cells inoculated in the subarachnoid space of the cat by injection into the cisterna magna survived as long as eleven days. When withdrawn after this length of time, and reinoculated into normal mice, the original tumor could be grown.

2. Repeated injections of suspensions of this tumor in the cisterna magna of cats appeared to produce increasing resistance to this tumor, as evidenced by a decrease in the viability of the tumor cells.

3. Foreign tumor cells inoculated in the subarachnoid space stimulated the arachnoid membrane to proliferate and shed phagocytic cells which attacked individual tumor cells. It is believed that this reaction may produce antibodies to the tumor; these antibodies may then be recovered from the cerebrospinal fluid.

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Intrathecal Inoculation of Mouse Sarcoma 180 in the Horse

PRODUCTION OF HETEROLOGOUS TUMOR ANTIBODIES

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REPEATED inoculations of suspensions of mouse sarcoma 180 into the cisterna magna of cats suggested the building up of some type of resistance on the part of the recipient animals.[18] This was shown by the decreasing viability of newly inoculated tumor cells as determined by the cerebrospinal fluid removed from the cats at intervals after such transitory heteroinoculations and injected into normal mice of the same strain in an attempt to grow the tumor.*

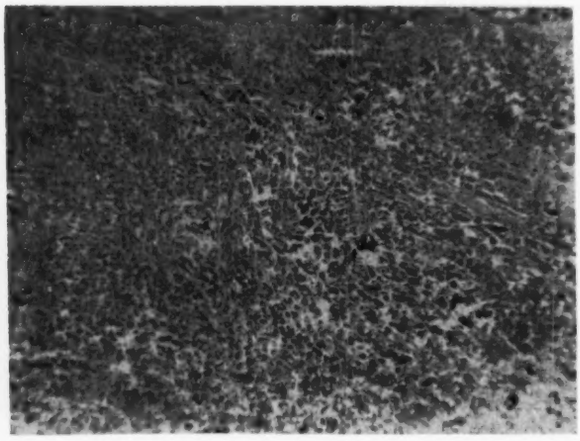


FIG. 1. Mouse sarcoma 180 from a very large, fifteen day old, healthy tumor (no central necrosis), resulting from the subcutaneous inoculation of 2 cc. suspension of seven, ten day old sarcoma 180/739A (Columbia University) tumors. This same suspension of multiple tumors was used for the second inoculations intraspinally of horses No. 2 and No. 3. Original magnification × 450.

Sarcoma 180 tumor cells injected into the subarachnoid space of cats survived as long as eleven days after a single inoculation; but when several inoculations were given at intervals, in the short period of two days after the last inoculation the cerebrospinal fluid failed to have any viable tumor cells or entities capable of growing a tumor.

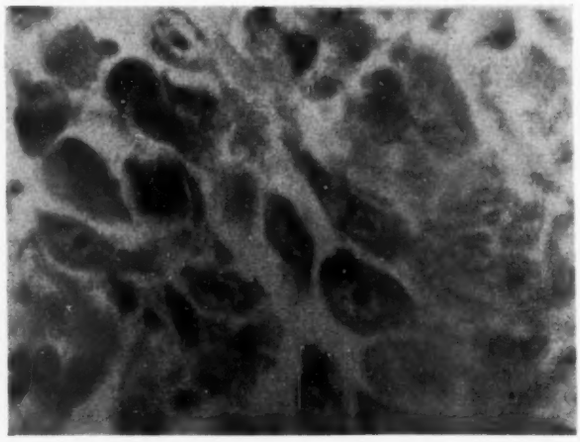


FIG. 2. Morphology of mouse sarcoma 180 cells used for intraspinal inoculation in horses; higher magnification of Figure 1. Original magnification × 1,000.

To determine if the intraspinal inoculation of tumor tissue results in the production of any antibodies, horses were immunized by repeated intraspinal injections of suspensions of mouse sarcoma 180. (Figs. 1 and 2.) Utilized in this determination were complement fixation tests on the cerebrospinal fluids of these immunized horses, and tracer experiments using radioactive I-131 combined with the immune cerebrospinal fluids.

That cancer cells contain some substance or substances of a chemical or biologic nature

* The preliminary experiments on cats were done by the author at the College of Physicians and Surgeons, Columbia University, New York, New York, where he formerly was Instructor in Anatomy, and Volunteer Worker in the Department of Cancer Research.

which make them different from normal cells is a commonly accepted belief. Some of these in the nature of viruses have been isolated from certain types of tumors or cancer.[19] It has been shown that there are contagious agents responsible for the development of antibodies against viruses, and that these contagious elements either by themselves or after undergoing variation are the cause of some cancers.[3] Although it has been most difficult to isolate and identify the qualitative chemical differences of malignant tissue, certain tumor lipids probably bound to proteins showing qualitative differences from those in normal tissues have been demonstrated by polarographic methods.[2]

The subject of tumor immunity was reviewed by Spencer in 1942,[17] and since that time there has been renewed and growing interest in this subject.

That it is possible to produce specific antibodies to a true antigen of cancer tissue and particularly to cancer cells has been shown by others using some of the usual routes of immunization together with agglutination tests, ring tests,[20] complement fixation tests or tracer experiments.[13] These investigations have important scientific value. However, the methods used have only academic interest thus far and have no practical value that might be applied to human beings with cancer since the antibodies so produced have been in small animals and in small quantities.

Heretofore the usual routes of immunization for the production of specific antibodies have been by the introduction of the foreign material or antigen into the animal body by intracutaneous, subcutaneous, intramuscular, intravenous or intraperitoneal injection or inoculation. The animal so treated produces antibodies locally and systemically, which may then be recovered from the blood of the animal with some difficulty. In these methods the blood cells have to be removed and the blood serum further refined by separating the antibodies from the other proteins in the serum. The specific antibodies are usually overshadowed by the presence of other antibodies.

In the experiments to be described the foreign antigen, mouse sarcoma 180, was introduced intraspinally into the subarachnoid space of horses, the recipient animals reacting thereto after one or more such inoculations and producing, as will be shown, specific antibody substances to the material inoculated. These antibody substances were recovered in a relatively simple manner from the watery cerebrospinal fluid of the animal so treated, and in relatively large quantities.

That the intraspinal route of immunization does indeed produce specific antibodies which can be recovered from the cerebrospinal fluid when bacteria (paratyphoid bacilli, Vibrio cholerae), tetanus toxin or sheep red corpuscles are used as the antigen, has been proved by others.[5,6,10–12] However, no one heretofore has used nucleated cells, particularly cancer tissue cells, as the antigen intraspinally, and no one heretofore has obtained and demonstrated that specific antibodies to the cancer tissue cells used as the antigen are recoverable from the cerebrospinal fluid of an animal so immunized.

THEORETIC AND ANATOMIC CONSIDERATIONS

Antibodies commonly found in the blood are not detectable in normal cerebrospinal fluid. Opsonins, important for phagocytosis, are usually absent. Most adult human beings have sufficient diphtheria antitoxin in their blood to protect them from the disease, but none of this antitoxin is present in the spinal fluid. Agglutinins and bacteriolysins for typhoid and various other bacilli are likewise usually absent from normal cerebrospinal fluid even in individuals immunized with typhoid vaccine and showing agglutinins in their blood serums in dilution as high as 1 : 100. Normal cerebrospinal fluid is usually devoid of these immunologic principles known to be present in the blood of all or most human beings.[8,14] The normal cerebrospinal fluid of animals is likewise believed to be devoid of any immunologic principles.

Virus synthesis, multiplication or proliferation appears to require intact functioning cells.[9] The intraspinal route of immunization allows for the introduction of any type of such already infected cells into a favorable fluid more or less confined to a cavity or space within the body, and for their survival for an appreciable time in the animal being immunized. During this time the infectious element or virus is able to survive, multiply and be released to maintain a continuing supply of antigenic material of a specific nature. The other usual routes of immunization do not offer these important advantages of intraspinal immunization.

The normal hematocephalic barrier appears to offer resistance to the passage of antigens

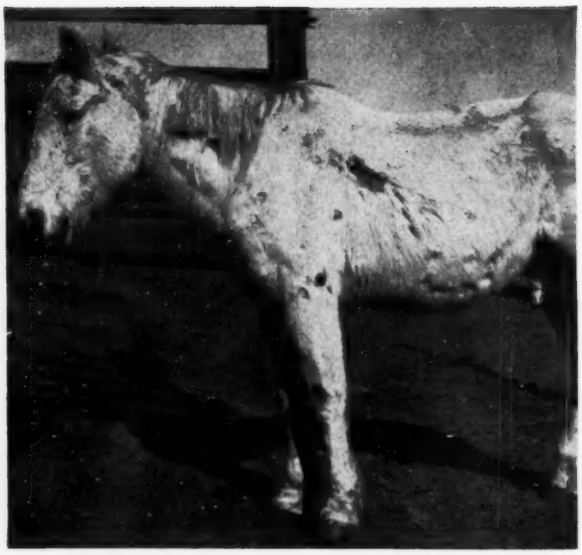


FIG. 3. Horse No. 1. First *trial* horse ever to receive an intracisternal inoculation of a suspension (5 cc.) of mouse tumor sarcoma 180/737A. Photograph taken immediately after the inoculation, December 30, 1947. Note the pre-existing melanosarcoma of the penis, multiple metastases and general inanition.

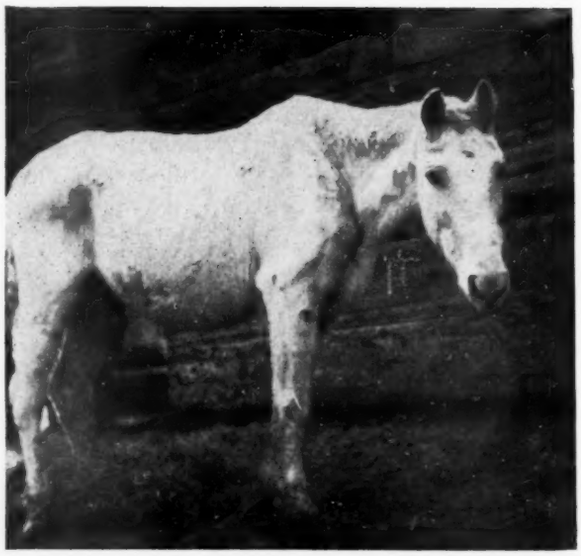


FIG. 4. Horse No. 1. Five days after the inoculation. This horse demonstrated the feasibility of intraspinal immunization with cancer cells, and was sacrificed two days later.

and antibodies only from the blood to the cerebrospinal fluid, and not the reverse.[4] When this barrier is disturbed by meningeal irritation, its permeability is increased, so that when antigens are introduced intraspinally they produce irritation and they may then appear in the blood in a few hours. Any antibodies thus produced systemically are then able to return to the cerebrospinal fluid through the now altered barrier,[15] thereby increasing the amount and concentration of antibodies locally produced in the subarachnoid space and recoverable from the cerebrospinal fluid.

The arachnoid membrane invests the brain and spinal cord, and although spread in a thin layer, collectively consists of an appreciable amount of tissue.[7] The larger the animal, the greater the amount of arachnoid membrane, the larger the subarachnoid space and the greater the amount of cerebrospinal fluid therein. The main cells comprising this membrane, which in places has many trabeculae forming a sponge-like arrangement, have potential phagocytic properties. The arachnoid membrane may well be considered as an associated part of the reticuloendothelial system recognized as the principle system which produces antibodies. It has been shown previously that in the presence of irritating and foreign substances these arachnoid cells bud off and become free, migratory, phagocytic cells in the cerebrospinal fluid.[1] Phagocytic cells of this type have been shown to produce antibodies after assimilating foreign substances.[16]

DESCRIPTION OF EXPERIMENTS

The insertion of a needle into the subarachnoid space of the horse in the region of the cisterna magna at the base of the skull, and the injection therein of a suspension of tumor cells would offhand appear to be a cruel, if not an impractical procedure. Such was not found to be the case after the very first trial inoculation was given to an old horse which had metastatic melanoma arising from the penis. (Figs. 3 and 4.) Using sterile precautions and local novocain® anesthesia preceding the small incision through the skin and subcutaneous tissues, the introduction of a spinal needle into the cisterna magna is practically painless. An increase and then sudden release of resistance are felt as the point of the needle passes through the more dense dura into the subarachnoid space, similar to that experienced in doing spinal taps on human beings. As with human subjects, this is sometimes accompanied with a very transitory reflex which is apt to make the horse move its head.

By using a throw-table it was possible to position the horse at the side of the table top with the latter in a vertical position, and to fasten the horse securely with broad straps

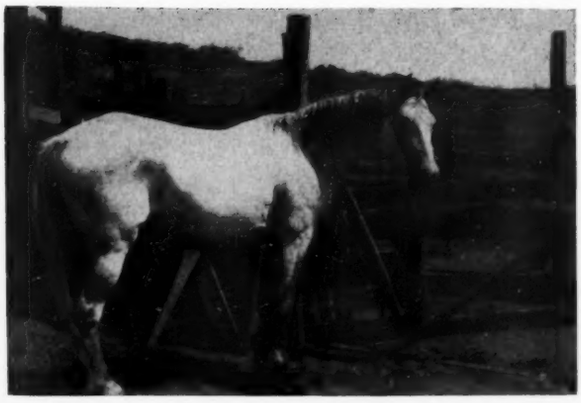


FIG. 5. Horse No. 6, a white gelding. Five weeks after the first and three weeks after the second cisterna magna inoculation of suspensions of mouse sarcoma 180 tumor tissue.

FIG. 6. Horse No. 6. Collecting the final immune cerebrospinal fluid (250 cc.) into an evacuated flask four weeks after the last of *five* cisterna magna inoculations of mouse sarcoma 180 suspensions given at intervals of 2, 3, 5 and 4 weeks, respectively.

before tilting the table top and horse to a horizontal position. The horse could then, on its side, be rotated in a horizontal plane to any position. With the horse in this fixed position the suboccipital region was shaved and properly sterilized for local anesthesia, insertion of the spinal needle and inoculation of tumor or withdrawal of cerebrospinal fluid.

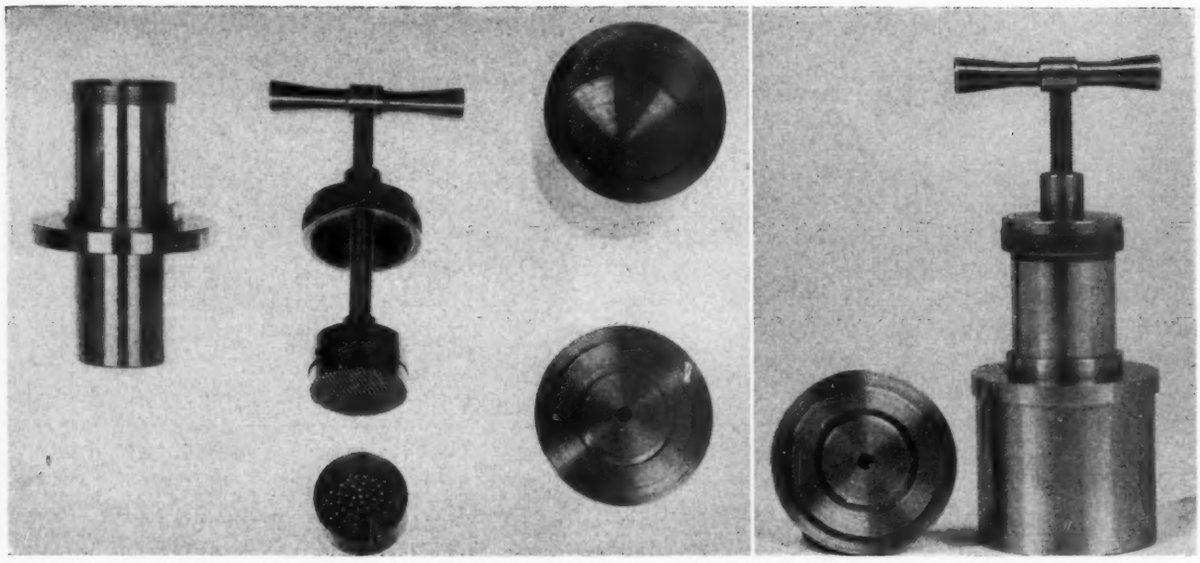
Horses tolerated such intraspinal inoculations of tumor suspensions very well. (Fig. 5.) Cerebrospinal fluid was collected either by drip, syringe or empty evacuated container. Using the empty evacuated flask, the maximum amount of fluid was obtained without exposure to or contamination by air. (Fig. 6.) As much as 400 cc. normal cerebrospinal fluid have been obtained by tap of the cisterna magna of the horse without deleterious effect.

The sarcoma 180 tumors were removed under sterile precautions from Longacre mice just before the inoculation. For the purpose of suspension of these tumor cells, innocuous fluids like distilled water or normal saline solution were suitable and used interchangeably. At first the tumors were ground up with the solution by using a mortar and pestle, but this did not yield a heavy enough suspension. A specially designed stainless steel grinding syringe was therefore used which produced a fairly thick suspension of practically all of the available tumor tissue. (Figs. 7 and 8.) Particular care was taken to use only healthy growing tumors which were neither ulcerating nor necrotic. The amount of tumor suspension varied from 5 to 20 cc. Ten cubic centimeters of a thick suspension was considered a good dose. For injecting, special 20 cc. Luer-Lok® syringes were used, the metal tips and glass stems of which were bored to gauge 12. Special 14 gauge, 4½ inch stainless steel Luer-Lok needles with stylets were found satisfactory. By combined use of these special instruments the tumor tissue suspensions were inoculated smoothly and without having either syringe or needle plugged by tissue during the procedure.

With proper facilities and correct technic, emphasis is again made that repeated tumor inoculations were tolerated very well by the horses. When the inoculation was given smoothly and without difficulty, the horse would often scamper off after being released or was frequently seen to eat its hay immediately and otherwise act normally. Inadvertent injury from the needle puncture may cause paralysis or ataxia of the legs which would prevent further use of the animal. This danger was reduced to a minimum by securely fastening the head and neck of the animal on the throw-table.

Before sacrificing the first trial horse seven days after it had received a single inoculation of 5 cc. suspension of sarcoma 180 tumor tissue, 40 cc. of clear cerebrospinal fluid were easily removed by cisternal tap. The protein content of this fluid was 60 mg. per cent; it contained an occasional red corpuscle; globulin was increased; culture for bacteria was negative; Wassermann reaction was reported negative. At autopsy, no blockage was found around the medulla or upper cervical cord. (Fig. 9.)

In contrast, sections of the medulla and cervical cord of horse No. 2 after *four* intra-



7 8

FIG. 7. Component parts of stainless steel grinding syringe: *Top, left to right:* barrel of syringe, open top and bottom (3.5 by 9.5 cm.), with sliding collar. Piston with grinding head and steel gasket; cap threaded on shaft. Over-all length of piston and head 12 cm.; diameter of head 3.1 cm. Receptacle (5.5 by 6 cm.); capacity 90 ml. *Bottom:* strainer (3.1 by 1.4 cm.) with holes 1 mm. in diameter. Cover (diameter 6 cm.) with grooves on undersurface showing, to fit both top of receptacle and barrel. Method: The open barrel with strainer inside bottom is set into the receptacle containing 20 ml. solution; the collar is adjusted to fit the top of the receptacle. The cancer tissue to be ground is dropped into the barrel and the piston is then inserted into the barrel. The top of the barrel is sealed by screwing on the cap. The piston is then advanced by turning the handle, thereby crushing the cancer tissue and grinding it through the holes in the strainer. The solution in the receptacle now contains the macerated cancer tissue. By unscrewing the cap and withdrawing the piston, the suspension of cancer tissue may be aspirated into the barrel and forced through the strainer again to get a more uniform suspension.

FIG. 8. Grinding syringe assembled. (Cover standing on edge.)

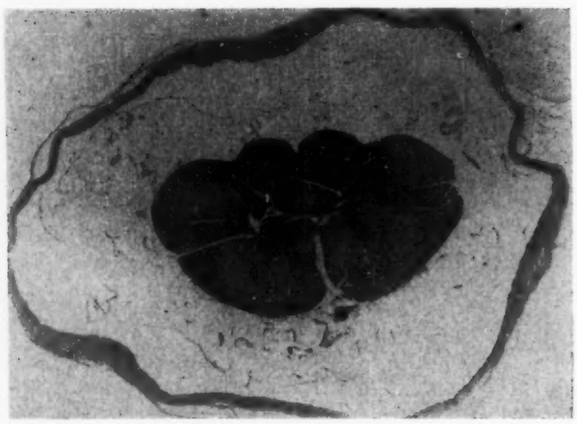


FIG. 9. Horse No. 1. Cross section of upper cervical cord seven days after a single intracisternal inoculation of 5 cc. suspension of mouse sarcoma 180 obtained from four 13 day old tumors. Note slight accentuation of trabeculae in the subarachnoid space, with no blockage. Original magnification × 4.

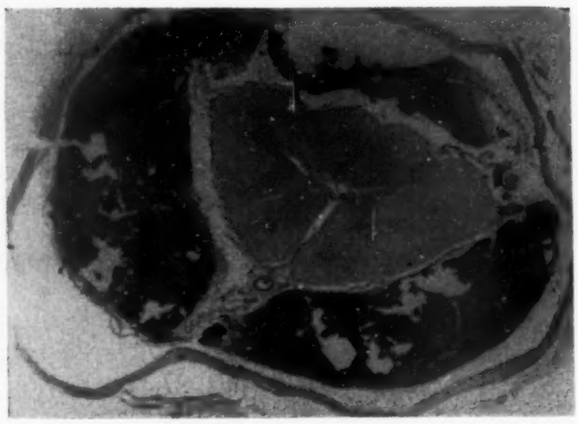


FIG. 10. Horse No. 2. Cross section of upper cervical cord five days after the last of four intracisternal inoculations given at two-week intervals. Note extensive blockage of subarachnoid space. Original magnification × 4.

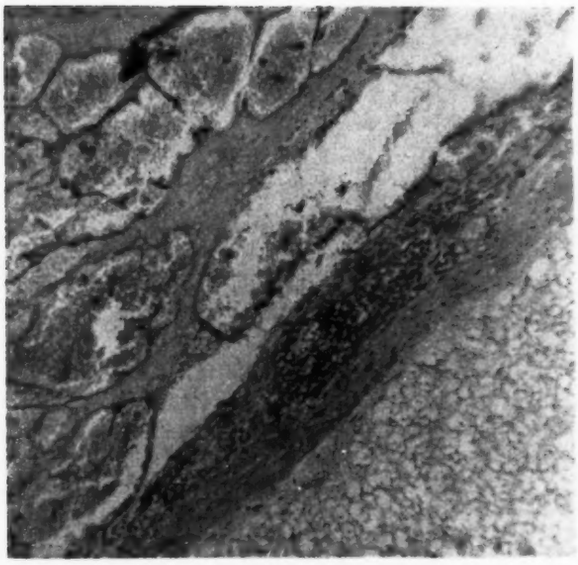


FIG. 11. Part of piarachnoid in Figure 10 showing focus of cellular reaction, thickening of arachnoid trabeculae and cellular accumulations in subarachnoid space. Note tendency of reaction to limit itself from the spinal cord proper. Original magnification × 450.

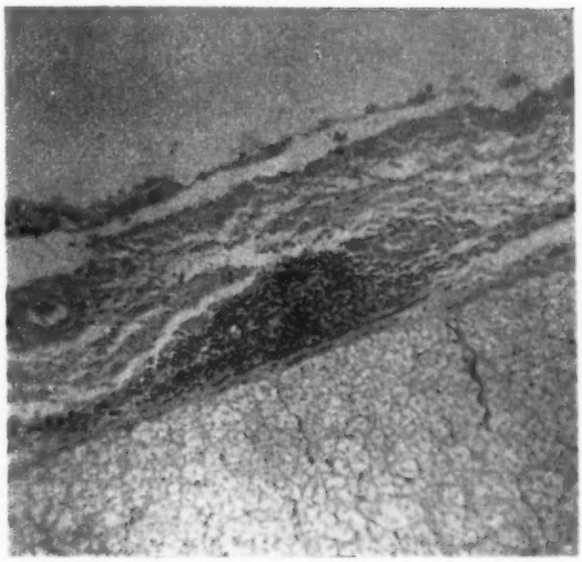


FIG. 12. Part of piarachnoid at a lower cervical level than shown in Figure 10. Note similar cellular reaction shown in Figure 11 but less involvement of the subarachnoid space and arachnoid "membrane." Original magnification × 450.

FIG. 13. Edge of piarachnoid focus of cellular reaction shown in Figure 12, showing tendency of proliferating arachnoid cells, fibroblasts and intercellular substance to wall off focus from the spinal cord proper. Original magnification × 1,000.

FIG. 14. Phagocytosis of mouse sarcoma 180 cell (largest cell, center) by detached arachnoid cells. Note arachnoid trabecula (diagonal structure), dormant arachnoid cell (lower portion of same), macrophages (near upper right corner), and cellular debris partly of cancer cells with accumulations of ghosts of red blood corpuscles in the spinal fluid. The arachnoid cell (large pale oval nucleus above and to the left of the larger cancer cell, center) appears to be still partly attached to the arachnoid trabecula. Compare center cancer cell with those shown in Figure 2. Original magnification × 1,000.

spinal inoculations of sarcoma 180 tumors intracisternally revealed what appeared to be a confined hemorrhage in the interstices of the subarachnoid space for a distance downward of approximately 4 inches from the foramen magnum. (Fig. 10.) This may have been traumatic from the last puncture and inoculation five days prior to autopsy, for, at the time of this last inoculation, which consisted of an unusually large quantity of suspension (20 cc.) of tumor tissue, 12 cc. of spinal fluid removed immediately before the inoculation showed no gross admixture of blood. However, in one slide was seen the actual escape of red cells from a broken capillary in the arachnoid region, so that this massive accumulation of red cells

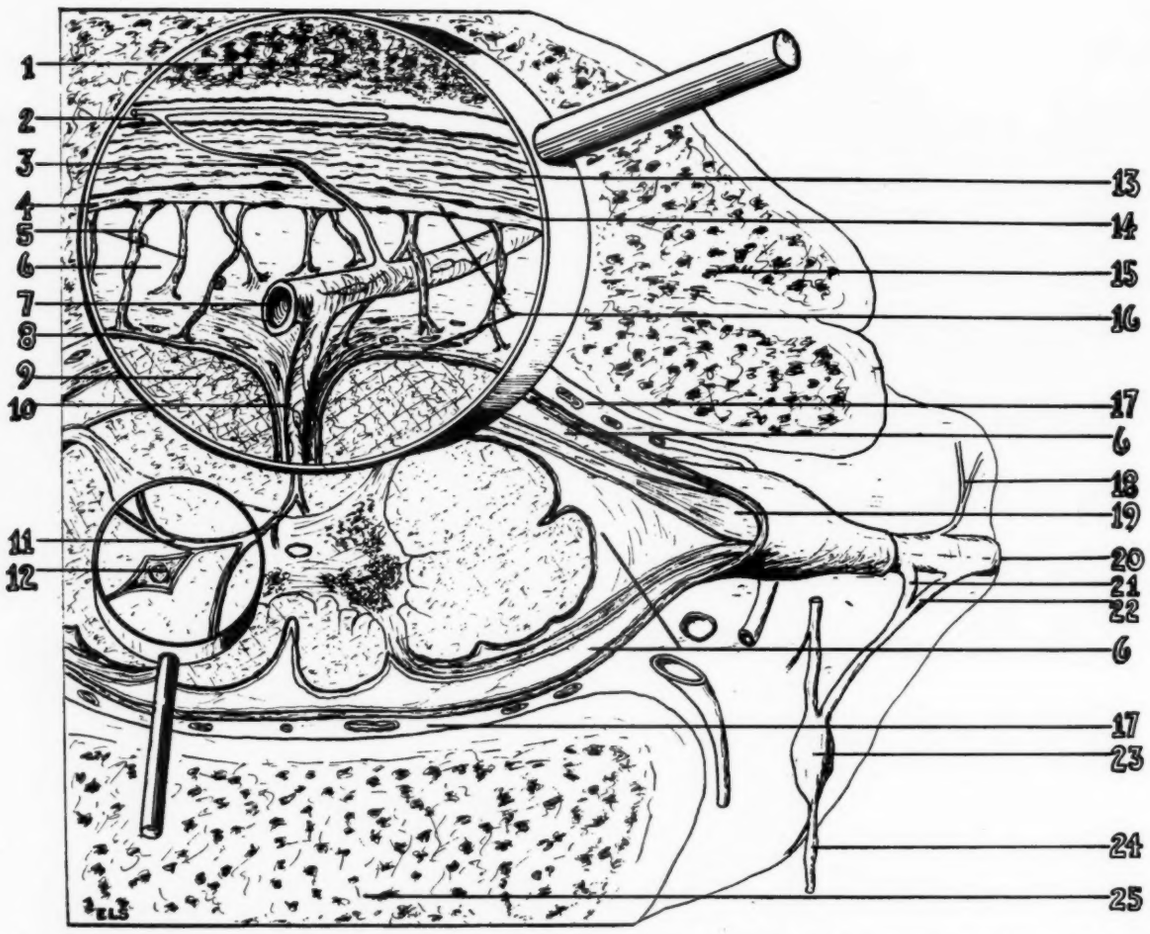


FIG. 15. Schematic drawing of the arachnoid-reticulomesothelial system in relation to the spinal cord and meninges, and to the general lymphatic system. (*1*) Lamina of vertebral arch (magnified); (*2*) epidural space with blood vessel; (*3*) blood vessel coursing through dura mater; note perivascular space continuous with subarachnoid space; (*4*) outer layer of arachnoid membrane attached to dura mater; (*5*) trabeculae coursing through subarachnoid space between outer and inner layers of arachnoid membrane; note dormant and budding arachnoid-reticulomesothelial cells; (*6*) spinal fluid in subarachnoid space; (*7*) blood vessel in subarachnoid space; note arachnoid cells covering the blood vessel; (*8*) inner layer of arachnoid membrane attached to pia mater; (*9*) spinal cord; (*10*) collateral blood vessel to spinal cord; note perivascular space continuous with subarachnoid space; (*11*) capillary within pericapillary space in grey matter of spinal cord (magnified); (*12*) nerve cell within perineural space; note continuity of perineural, pericapillary, perivascular, subarachnoid and transdural perivascular spaces, the last of which connects with the epidural lymphatics draining into the segmental prevertebral lymph nodes; (*13*) dura mater; (*14*) subdural space; (*15*) lamina of vertebral arch; (*16*) arachnoid membrane enclosing subarachnoid space and spinal fluid; (*17*) blood vessels, lymphatics and fatty tissue in the epidural space; (*18*) posterior branch of peripheral nerve; (*19*) spinal ganglion of posterior root; (*20*) anterior branch of peripheral nerve; the nerve roots, and to a lesser extent the common nerve inside its dural extension covering, are invested by arachnoid membrane, forming possible channels of communication with the prevertebral lymphatics; (*21*) white ramus communicans; (*22*) grey ramus communicans; (*23*) ganglion of the sympathetic nervous system; (*24*) communicating branch in sympathetic chain of ganglia; (*25*) body of vertebra.

in the subarachnoid space may have been the result of a type of hemorrhagic arachnoiditis.

Distinctive foci of cellular reaction were seen in scattered areas in the thickened and inflamed piarachnoid (Fig. 11), especially in the upper cervical areas. At a lower cervical level the reaction was less intense, the accumulation of red cells in the subarachnoid space much less evident, but the cellular accumulations in the piarachnoid were still found. (Fig. 12.) These inflammatory foci appeared to be somewhat walled off from the cord substance proper by proliferating fibroblasts and arachnoid cells. (Fig. 13.) The centers of these cellular foci

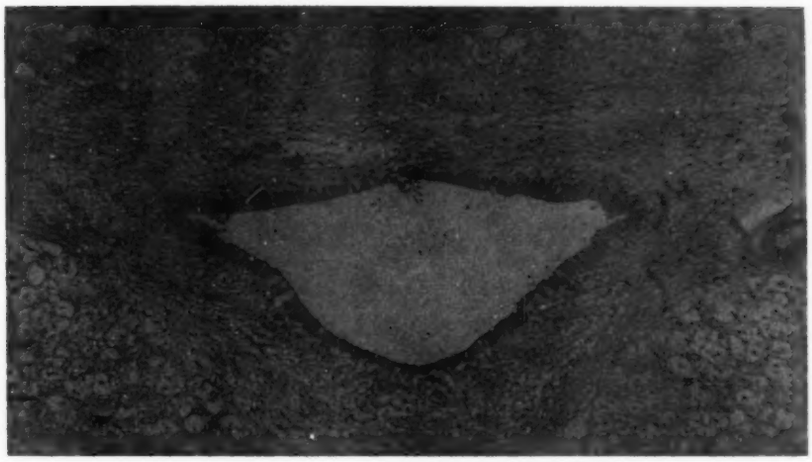


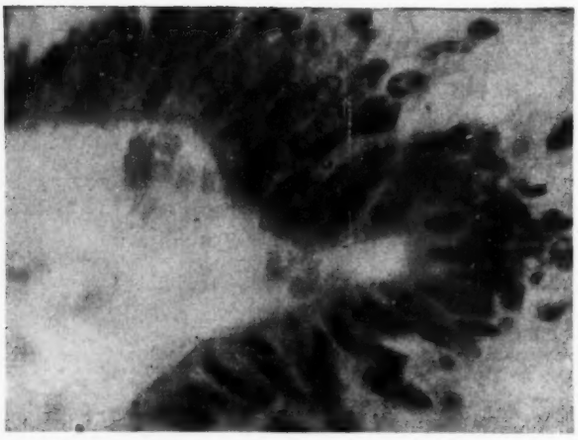
FIG. 16. Central canal of spinal cord, horse No. 2, upper cervical region. Note absence of nucleated cells in spinal fluid filling same, and proliferation of lining ependymal cells causing hypertrophied folds of this lining at each angle. Original magnification × 450.

appeared to be accumulations of monocytes, macrophages (clasmatocytes), some leukocytes and lymphocytes, and an occasional isolated or small group of cancer cells having large, oval, dark-staining chromatic nuclei with multiple nucleoli. In some of these areas, the cancer cells appeared to be dead since they were irregular, angular-shaped and diffusely stained black.

The trabeculae comprising the tissue of the arachnoid membrane appeared thickened. Figure 14 shows one of these thickened trabeculae (diagonal structure), on the lower half of which is a still attached mesothelial arachnoid cell. Normally these cells are dormant; however, in the presence of introduced foreign red corpuscles or other particulate matter (India ink) or chemicals (like thiamine hydrochloride), they become stimulated to enlarge, become sessile and then to bud off and become free circulating cells in the cerebrospinal fluid filling the subarachnoid space. These cells were described by Key and Retzius in their monographs published as far back as 1873. Figure 14 shows beyond a reasonable doubt the phagocytosis of a single sarcoma 180 cancer cell by several of these free arachnoid cells, one of which appears to have been attracted from its place of origin on the nearby trabecula. These free, "wandering" or rather circulating arachnoid cells have now acquired phagocytic properties, as described in the first article.[18] They may well be termed arachnoid mesothelial monocytes, macrophages or clasmatocytes according to the stage of their activity. At the height of this activity the shedding of exoplasm after the ingestion and assimilation of cancer cells should correspond with the liberation of specific antibody globulin(s) to the cancer cells, which antibodies are then incorporated into the cerebrospinal fluid. The complete dissolution of these clasmatocytes should also liberate antibodies. Many of these activities have been personally observed in hanging drops of cerebrospinal fluid removed during the process of intraspinal immunization using sarcoma 180 as the antigen, and when stained supravitally or fixed in iodine vapor.

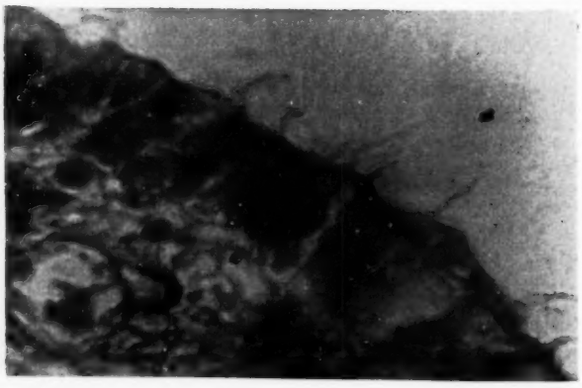
One must infer that the arachnoid mesothelial cells are the source of at least part of the globulin clinically found in the cerebrospinal fluid in infections and pathologic conditions involving the meninges and/or the central nervous system. In some instances clinically, these free mesothelial cells may assume a rounded form in the cerebrospinal fluid and hence may be counted in with, and misinterpreted as, lymphocytes in doing cell counts of spinal fluid. It is believed that the arachnoid mesothelial cells may produce part of the globulin in cerebrospinal fluid, particularly in early pathologic conditions, and that the antibody globulin recovered from the cerebrospinal fluid represents the synthesis of a new kind of protein largely by these cells when under the influence of an antigen. Hence the definition of an antigen may be expanded to include any substance which can specifically modify the synthesis of the cytoplasm of the arachnoid mesothelial cells.

The formation of antibodies by the shedding



A

B



C

FIG. 17A, B and C. Proliferating ependymal cells lining central canal of horse No. 2. Note the *ciliated* surface cells and the active multiplication and migration of other ependymal cells into the cord substance. Original magnification × 1,000.

of parts of the cytoplasm of phagocytic macrophages of the reticuloendothelial system after the ingestion and assimilation of the antigen (a red dye–stained protein) was described by Sabin.[16] In order to emphasize the importance of the arachnoid membrane and its mesothelial cells in the defense of the body especially of its nervous system, and to differentiate it from the reticuloendothelial system of the rest of the body, particularly from the lymphatic system, it is proper to refer to this mechanism as the arachnoid-reticulomesothelial system. (Fig. 15.) The term mesothelial is used since the arachnoid membrane is derived from ectodermal (epithelial) mesoderm.

An interesting observation in studying the *central* canal in many sections of the spinal cord from the medulla caudad in horse No. 2 was the absence of any nucleated cells in the spinal fluid within the canal, although the subarachnoid space particularly near the medulla was packed with them. The ependymal cells lining the central canal in the horse are ciliated. (Figs. 16 and 17A, B and C.) Other ependymal cells showed active proliferation, with wandering of the newly formed cells outward into the gelatinous area around the central canal and into the cord substance. (Ciliated lining ependymal cells have been described in man, usually in young individuals.) In view of the absence of foreign nucleated cells within the central canal, the concept is presented that the function of the ciliated ependymal cells is to aid in the circulation of the spinal fluid within the canal in a cephalad direction. Such a current of fluid, together with the action of the cilia, would tend to prevent the passage of substances in the opposite direction.

The perivascular spaces around the blood vessels in the arachnoid membrane appeared loaded with cells, especially in the region of the dorsal median septum. The thickened dura also showed some perivascular accumulation of cells, and a suggestion of foci of cellular accumulations similar to those in the piarachnoid in the region of the subdural space.

The pathologic reaction following intracisternal inoculation of suspensions of mouse sarcoma 180 in the horse showed comparable changes in the meninges observed in similar experiments in the cat and dog (Stern, p. 507). The extreme reactions noted in the horse can be minimized by regulating the dosage of the

suspensions inoculated, as well as the intervals between the inoculations. For example, in horse No. 6, which received a total of *five* inoculations, 125 cc. of *clear spinal fluid* were readily obtained by cisternal tap four days after the last inoculation, and another 125 cc. of slightly bloody spinal fluid were obtained following an immediate second cisternal tap with a second needle. Just how many inoculations an individual horse might tolerate with properly adjusted dosages and time intervals between inoculations remains to be determined.

Six horses and two control horses were used in these experiments. One to five inoculations of tumor suspensions were given at intervals of five to thirty-five days. Usually clear spinal fluid was obtained at the time of each tap; occasionally the fluid would be slightly blood-tinged. From 5 to 20 cc. of fluid were usually removed, and the inoculation then given into the cisterna magna without disturbing the position of the needle. For the collection of final cerebrospinal fluids by empty evacuated containers as much as 250 cc. were easily obtained without exposure to air. With repeated tappings, the final yield of fluid undoubtedly could have been increased. All fluids were usually centrifuged at 4,500 r.p.m. for half an hour and any sediment was removed before the fluids were refrigerated until utilized or lyophilized. (Fig. 18.)

FIG. 18. Comparative amounts of lyophilized cerebrospinal fluid finally obtained from immunized horse No. 6 (right) and from normal control cerebrospinal fluid from horse No. 10C. Each vial represents 15 cc. of original fluid. The vial on the right contains the specific mouse sarcoma 180 antibodies produced by the intraspinal route of immunization.

COMPLEMENT FIXATION TESTS

Sixteen tumor inoculations were given to the six horses. Tables I and II outline the significant data of these inoculations. The spinal fluids from immunized horses Nos. 2, 3 and 6 were used in complement fixation tests. It is well known that complement fixation tests are extremely sensitive and are commonly used for the detection of specific antibodies.

The application and standardization of the complement fixation test applied to these cerebrospinal fluids was complicated by finding anticomplementary bodies (Table II, *A*) and also a fixation for both tumor and normal heart antigens (*B*). With increasing immunization (*C*), however, an increase in fixation with tumor antigen over normal heart antigen was found. Finally with the greatest degree of immunization (*D*) using extracts from antigens frozen with liquid nitrogen and pulverized, a specific fixation was demonstrated with tumor antigen over and above that produced with normal heart and connective tissue antigens. The control cerebrospinal fluid tests gave negative results.

Complement fixation tests were performed according to the method of Kolmer using anti-sheep amboceptor supplied by the California State Division of Laboratories, preserved sheep cells and guinea pig complement. Complement titer was determined before each test and the usual controls were included. In the first tests the following antigens were employed: (A) an aqueous extract from ground-up Longacre mouse sarcoma 180, and (B) a 95 per cent ethyl alcohol extract of this tumor. For each extract a good-sized fifteen day old tumor approximately 1.5 cm. in diameter and showing

TABLE I

SCHEDULE OF HETEROINOCULATIONS, PROGRESSIVE IMMUNIZATION OF HORSES TO SARCOMA 180 BY THE INTRASPINAL ROUTE

Horse	No. of Tumors	Generation	Age of Tumors (days)	Diluent H_2O (cc.)	Suspension Injected (cc.)	Interval of Injections (wk.)
No. 3	4	738A	12	15	8	..
	7	739A	10	30*	10	2
No. 2	4	738A	12	15	5	..
	7	739A	10	30*	10	2
	7	740A	11	20	10	2
	8	740B	18	20	20	2
No. 6	2	746B–S_1	12	10	6	..
	2	746B–S_2	11	10	8	2
	4	753B	11	10	10	3
	8	755B	11	10	10	5
	5	755B–S	25	20	12	4

* Normal saline.

TABLE II

COMPLEMENT FIXATION TESTS—PROGRESSIVE IMMUNIZATION OF HORSES TO SARCOMA 180 BY THE INTRASPINAL ROUTE

Horse	No. of Inoculations	Days after Last Inoculation	Cerebrospinal Fluid Removed (cc.)	Total Protein (mg. %)	Complement Fixation Tests
No. 3	2	4	125	100	*A*—Anticomplementary; no further fixation after removal of anticomplementary bodies
No. 2	4	5	80	...	*B*—Positive fixation for tumor and normal heart antigens; higher concentration of complement-fixing antibodies in cerebrospinal fluid than in blood serum
No. 6	4	28	170 (No. 6)	98	*C*—Increased fixation with tumor antigen over normal heart antigen
	5	28	250 (No. 7)	204	*D*—Specific fixation with tumor antigen over normal heart and connective tissue antigens
			Controls		
No. 5	..	..	185	...	Negative cerebrospinal fluid and blood serum
No. 10c	..	..	150	43	.....
No. 11c	..	..	95	52	Negative cerebrospinal fluid

no gross necrosis was removed from a female Longacre mouse which had received a subcutaneous injection of a mixture of ground-up healthy tumors from seven transplants of sarcoma 180 which were ten days old (739A male Longacre mice). Biopsies of each tumor were kept in 10 per cent formalin. Double distilled water, 15 cc., was used in making the aqueous extract; 15 cc. grain alcohol (190 proof) was used in making the alcohol extract.

Assay No. 1

The horse identified as No. 3 was used and 15 cc. of cerebrospinal fluid were removed immediately prior to the inoculation. Mouse sarcoma 180 of generation 738A was used in which the tumors were twelve days old. Four tumors were macerated in 15 cc. of distilled water, and 8 cc. of the mixed suspension were injected into the cisterna magna of the horse. Fourteen days later 2 cc. of cerebrospinal fluid were removed and the first injection was repeated with mouse sarcoma 180 ten days old. Seven tumors were macerated in 30 cc. of normal saline solution and a suspension of 10 cc. was administered via the same route.

The following protocol was followed for the determination of the optimum dose and antigenic unit. Using 125 cc. of cerebrospinal fluid from horse No. 3 removed eighteen days after the first inoculation and four days after the second inoculation of tumor, it was then concentrated to one-fourth volume by desiccation over anhydrous $CaCl_2$ at room temperature, for "immune" spinal fluid.

AQUEOUS ANTIGEN A

"Immune" Spinal Fluid Dilution	Antigen Dilution					
	Full	1:2	1:4	1:8	1:16	1:32
Full	4+	4+	4+	4+	4+	4+
1:2	4+	4+	4+	4+	4+	4+
1:4	0	0	1+	2+	3+	2+
1:8	0	0	0	0	0	0

ALCOHOLIC ANTIGEN B

"Immune" Spinal Fluid Dilution	Antigen Dilution					
	Full	1:2	1:4	1:8	1:16	1:32
Full	2+	4+	4+	4+	4+	4+
1:2	2+	4+	4+	4+	4+	4+
1:4	2+	4+	3+	2+	1+	1+
1:8	2+	4+	0	0	0	0

Further complement fixation tests using the concentrated spinal fluid from horse No. 3 showed the spinal fluid to be anticomplementary and it was treated with N/300 HCl to remove anticomplementary substances. However, further determinations showed no fixation indicating that the treatment for the removal of the anticomplementary substances may also have removed the small amount of specific antibodies that may have been present.

Assay No. 2

From the horse identified as No. 2, 10 cc. of cerebrospinal fluid were removed first. Four mouse sarcoma 180 tumors which were twelve days old were macerated with 15 cc. of distilled water, and 5 cc. of the thick suspension were injected into the cisterna magna. Fourteen days after the first injection 3 cc. of spinal fluid were removed. Seven tumors of the same type which were ten days old were macerated with 30 cc. of normal saline solution forming a thick suspension, and 10 cc. were administered. Fourteen days after the second injection 10 cc. of spinal fluid were removed; seven tumors eleven days old were macerated with 20 cc. of distilled water to form a thick suspension. Ten cubic centimeters of the suspension were administered. Fourteen days after the third injection 12 cc. of spinal fluid were removed. Eight tumors which were eighteen days old were ground with 20 cc. of distilled water and 20 cc. of the suspension were administered.

Complement fixation test was then done on spinal fluid from horse No. 2 removed five days after the last inoculation. The aqueous tumor antigen A (described in section Complement Fixation Tests) sarcoma 180 in concentration of 1:4 as determined by previous titrations for the optimum dose was used.

Normal spinal fluid from horse No. 5 was used as a control and showed no complement fixation.

Spinal Fluid Dilution	Complement Fixation
1:4	2+
1:8	1+
1:16	0
1:32	0

The foregoing test was the first determination showing definite complement fixation, and the following tests were performed in an attempt to establish the identity and distribution of the complement-fixing antibodies.

Both blood serum and immune spinal fluid from horse No. 2 were tested using aqueous tumor antigen sarcoma 180, antigen A and aqueous normal mouse heart antigen. This latter antigen was prepared by grinding up the heart, after bleeding, of a normal female Longacre mouse with 15 cc. double distilled water. Normal horse spinal fluid and blood serum were used for controls.

	Tumor Antigen (Spinal Fluid or Serum Dilution)			Normal Heart Antigen (Spinal Fluid or Serum Dilution)		
	Full	1:2	1:4	Full	1:2	1:4
Spinal fluid, immunized	4+	4+	4+	4+	4+	4+
Spinal fluid, normal	0	0	0	0	0	0
Serum immunized	4+	1+	0	2+	1+	0
Serum, normal	0	0	0	0	0	0

These complement fixation determinations showed the existence of a definitely higher concentration of complement-fixing antibodies in the spinal fluid than in the blood serum following intrathecal administration of tumor antigen. However, the identity of the antibodies was not definitely established since there was apparently an equal amount of fixation with each of the test antigens. Normal spinal fluid and blood serum of the horse contained no anti-mouse antibodies. Probably the minimum amount of immunization necessary for the

demonstration of antibodies is that which was given horse No. 2.

Assay No. 3

A horse identified as No. 6 was used in this assay. Twenty cubic centimeters of cerebrospinal fluid were taken before the first injection. Two tumors of sarcoma 180 were used which were twelve days old. The tumors were macerated with 10 cc. of distilled water and 6 cc. of the suspension were administered. One cubic centimeter of spinal fluid was removed prior to the second injection. Two tumors eleven days old were macerated with 10 cc. of distilled water to form the suspension and 8 cc. of this were administered fourteen days after the original inoculation. Twenty-one days after the second inoculation (Fig. 5) 10 cc. of spinal fluid were removed. Four tumors eleven days old were macerated in 10 cc. of distilled water to form a thick suspension and 10 cc. of the suspension were administered. Thirty-five days after the third inoculation 11 cc. of spinal fluid were removed: Eight tumors eleven days old were macerated with 10 cc. of distilled water and 10 cc. of the suspension were injected. Twenty-eight days after the fourth inoculation 170 cc. of spinal fluid were removed and labeled Spinal Fluid No. 6. Five tumors twenty-five days old were ground with 20 cc. of water and 12 cc. of the suspension were administered. The spinal fluid labeled No. 6 was lyophilized in 1 ounce bottles.

The lyophilized spinal fluid from horse No. 6, ninety-eight days after the first inoculation of tumor, eighty-four days after the second, sixty-three days after the third and twenty-eight days after the fourth inoculation, was used for complement fixation tests. This lyophilized immune spinal fluid was reconstituted by diluting with distilled water to give five times the concentration of the original spinal fluid, and was adsorbed with normal mouse heart antigen. Using aqueous tumor antigen A:

Concentration of Spinal Fluid Concentrate	Immune Spinal Fluid	Control Spinal Fluid
	Anticomplementary	
1:2		
1:4	4+	2+
1:8	4+	1+

Using normal mouse heart antigen:

Concentration of Spinal Fluid Concentrate	Immune Spinal Fluid	Control Spinal Fluid
	Anticomplementary	
1:2		
1:4	2+	2+
1:8	1+	1+

These determinations showed a definite increase of complement fixation titer using tumor antigen over that found using normal heart antigen. The possibility that the increase of titer may have been due to tissue specificity rather than the antigenic difference between tumor and normal tissue was entertained since tumor antigen is produced from connective tissue primarily, and the normal mouse antigen used was produced largely from heart muscle.

Further tests were therefore made, using the final lyophilized spinal fluid from horse No. 6 labeled Spinal Fluid No. 7 which was removed 126 days after the first tumor inoculation, 112 days after the second, 91 days after the third, 56 days after the fourth, and 28 days after the fifth inoculation. (Fig. 6.) The lyophilized normal spinal fluid from horse No. 11c was used as control.

The following antigens were used: (1) aqueous tumor antigen A; (2) normal mouse heart antigen; (3) normal mouse connective tissue antigen, derived from subcutaneous abdominal parieties.

The lyophilized spinal fluids were restored with sterile distilled water to give a final concentration of five times the original fluid, i.e., 15 cc. spinal fluid lyophilized were restored with 3 cc. distilled water.

Complement fixation tests were set up using the restored fluids in a dilution of 1:8, the maximum amount of spinal fluid giving no anticomplementary effects as determined by previous titrations.

Antigens	Immune Spinal Fluid No. 7	Normal Spinal Fluid
Aqueous tumor antigen A.....	4+	0
Normal heart antigen.....	0	0
Normal connective tissue antigen	0	0

This test was repeated two weeks later, using newly standardized reagents, with the following results:

Antigens	Immune Spinal Fluid No. 7	Normal Spinal Fluid
Aqueous tumor antigen A.....	3+	0
Normal heart antigen.....	0	0
Normal connective tissue antigen	0	0

The results in both of the foregoing tests indicate a definite specificity of the antibodies in Spinal Fluid No. 7 for the tumor antigen.

The apparent absence of anti-mouse (heart) antibodies is due to the fact that the titration of reagents was adjusted to give negative fixation with normal heart antigen in order to detect fixation over and above that produced by normal mouse antibodies.

In order to be positive of a normal connective tissue antigen of adequate strength containing a maximum of proteins, the connective tissue for the following tests was pulverized in a frozen state using liquid nitrogen. The tumor antigen was likewise frozen with liquid nitrogen and ground finely with a mortar and pestle, in order to produce a more complete extraction of antigen material.

Antigens	Immune Spinal Fluid No. 7	Normal Spinal Fluid
Aqueous tumor antigen "A"....	4+	0
Connective tissue antigen.....	(doubtful)	0

This test corroborated the previous findings.

To determine the thermolability of the antibodies, complement fixation tests on the immune spinal fluid were made as follows:

The immune spinal fluid was heated at 56°C. for thirty minutes and 120 minutes. Complement fixation tests were made on the heated and unheated spinal fluids using normal spinal fluid as a control. Aqueous tumor antigen A was used throughout.

Spinal Fluid	Immune Spinal Fluid No. 7	Normal Control
Spinal fluid, unheated.....	4+	0
Spinal fluid, heated 30 min.....	2+	0
Spinal fluid, heated 2 hr.....	0	0

These results show a reduction to one-half of the complement fixation properties of the antibodies after heating for thirty minutes at 56°C., and complete loss after heating for 120 minutes at the same temperature. These tests appear to rule out the possibility of the complement fixation as having been due to non-specific reaction caused by any possible accelerator globulin activity of the immune spinal fluid upon the thromboplastic properties of the tumor tissue extract. Any such accelerator globulin activity would be expected to have persisted in spite of the heating of the immune spinal fluid to 56°C. and would have given continued complement fixation, which was not the case.

Electrophoretic analysis of immune Spinal Fluid No. 7 was done by dissolving the lyophilized material from 90 cc. of spinal fluid in 50 cc. of water, which was then dialyzed against 1.0 per cent saline. This solution gave a protein analysis (Nessler's) of 0.45 per cent. It was then concentrated to approximately 1.4 per cent and tested for antibodies against normal and tumor mouse tissue. Ring tests as well as macroprecipitation tests over a wide range of antigen dilutions were consistently negative. The remaining spinal fluid was then analyzed by electrophoresis. This showed a considerable amount of an albumin-like protein as well as globulin. The latter showed no distinctive boundaries as is obtained in serum. (Fig. 19.)

The antibodies found by complement fixation tests most likely were represented in the globulin portion demonstrated in the electrophoretic analysis. These antibodies may not have been sufficiently concentrated in the aforementioned ring tests or macroprecipitation tests which are considered much less sensitive than the complement fixation tests. Moreover, the negative ring and macroprecipitation tests may indicate that either antigen and/or antibodies possessed univalent combining sites as regards their

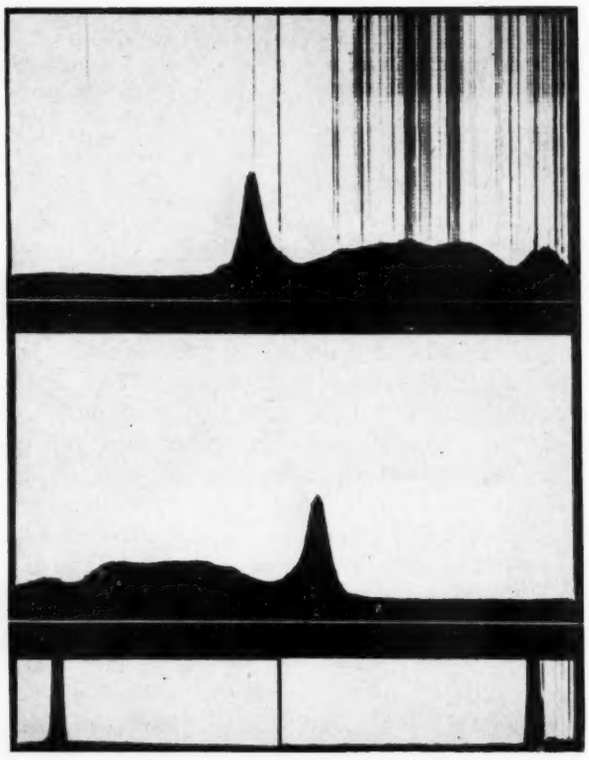


FIG. 19. Composition of the immune cerebrospinal fluid obtained from horse No. 6, as shown by electrophoretic analysis. Larger peak represents albumin-like protein; the lower elevations represent globulin (antibodies).

lattice structures, which would account for a non-flocculating combination.[14]

The protein content of immune Spinal Fluid No. 7 was 204 mg. per cent; those of the normal control spinal fluids were found to be 43 and 52 mg. per cent.

TRACER EXPERIMENTS

Besides the complement fixation tests which have been described, tracer experiments were made with immune Spinal Fluid No. 7 four years after its collection and lyophilization. (Fig. 18.) Normal spinal fluid was used for a control. An iodination procedure was carried out on both the lyophilized immune and control spinal fluids after reconstituting in isotonic saline, using radioactive I-131 in a KI-I$^-$ mixture. The unwanted iodine and dialyzable constituents were removed from these mixtures by dialysis.

Both the immune and control spinal fluids were injected into mice and rats bearing tumors. It was necessary to filter the tagged immune fluid through cotton in order to remove insoluble tagged, non-dialyzable organic material of a protein or conjugated protein nature prior to its administration. The I-131–tagged materials were given intravenously via the external jugular vein. The dose to the mice was 0.1 cc. of the reconstituted spinal fluid containing 0.1175 microcuries I-131. The rats were given 0.5 cc. Paris mice were used bearing eleven day old tumors, sarcoma 180, generation No. 36, this tumor being the same type used to produce the immune spinal fluid. In addition, fifteen mice of a Swiss albino strain were tested with the two spinal fluids. These animals were bearing spontaneous tumors of an entirely different type, which in most instances were mammary carcinoma. The materials were also tested on rats bearing transmissible lymphosarcoma. All of the animals were sacrificed four hours after the administration of the I-131–tagged material. The data are expressed as the percentage of the dose found per gram wet weight of tissue.

TABLE III

TRACER EXPERIMENT—DISTRIBUTION OF I-131–TAGGED ANTISARCOMA 180 IMMUNE AND CONTROL HORSE CEREBROSPINAL FLUIDS AFTER INTRAVENOUS INJECTION IN MICE BEARING SARCOMA 180 TUMORS

Tissue	Per cent of Dose per Gram Wet Weight after 4 Hours	
	Immune Spinal Fluid No. 7 (Averages, 10 Animals)	Control Spinal Fluid (Averages, 7 Animals)
Kidney	6.81	6.44
Gastrointestinal tract	3.74	4.40
Liver	2.15	9.89
Skin	3.34	2.72
Spleen	6.36	21.21
Balance of animal (muscle and bone)	3.11	2.68
Urine	14.1	21.8
Tumor (sarcoma 180)	15.9 (Range 3.0%–41.0%)	1.21 (Range 0.2%–2.43%)

The immune spinal fluid demonstrated a specificity for the mouse sarcoma 180. (Tables III to VI.)

The deposition of immune and normal control spinal fluid as denoted by the I-131 tag in mice bearing sarcoma 180 was observed to be similar in normal non-malignant tissues with the exception of spleen which showed a high uptake with the iodinated normal control spinal fluid for some unknown reason.

The deposition of the immune and normal control spinal fluids as denoted by the I-131

tag in the various types of tumors was as follows:

Types of Tumors	Sarcoma 180 Immune Spinal Fluid	Control Spinal Fluid
Mouse sarcoma 180 tumors.....	15.9 % (10 animals)	1.21% (7 animals)
Mouse spontaneous tumors (carcinoma)....	1.82% (10 animals)	2.14% (5 animals)
Rat lymphosarcoma....	0.21% (2 animals)	0.36% (2 animals)

These tracer experiments corroborated the specificity of the sarcoma 180 tumor antibodies in the cerebrospinal fluid of the horse immunized by the intraspinal route, as was previously shown by the complement fixation tests. It should be stressed that both complement fixation tests and tracer experiments were done at separate and unrelated laboratories with which the writer had no affiliations. The exact findings of these tests have therefore been recorded in an absolute impartial and unbiased manner.

COMMENTS

A practical method to produce specific antibodies to cancer tissue (mouse sarcoma 180) in large quantity by the intraspinal route of immunization in large animals like the horse has been described. The details of complement fixation tests and tracer experiments have been given to demonstrate such specificity.

The prevailing opinion regarding the intraspinal route of immunization when bacteria or toxins are used is that this method is a dangerous procedure and is apt to cause severe meningitis and death. This view is justifiable and particularly true when small animals have received such immunization. This route of immunization is not used in man, nor are vaccines given intraspinally, for this reason.[21] Because of this existing knowledge very little has been done in further investigating the possibilities of such immunization.

A thorough search of the literature and direct inquiry to veterinary colleges and pharmaceutical laboratories preparing vaccines in this country failed to reveal any information on the practicability of using large animals like the horse for intraspinal immunization. Nucleated cells, particularly cancer cells, have never before been used as the antigen intraspinally.

The theoretic and anatomic considerations of intraspinal immunization have been discussed.

TABLE IV

TRACER EXPERIMENT—INDIVIDUAL READINGS FOR THE UPTAKE BY SARCOMA 180 TUMORS FOUR HOURS AFTER INTRAVENOUS INJECTION OF I-131–TAGGED ANTISARCOMA 180 IMMUNE AND CONTROL HORSE CEREBROSPINAL FLUIDS*

Per cent of Dose per Gram Wet Weight of Tumor (Sarcoma 180)	
Immune Spinal Fluid No. 7	Control Normal Spinal Fluid
19.94	0.28
12.02	0.94
3.41	0.47
3.77	0.79
5.91	2.43
6.56	2.12
23.42	1.44
41.22	....
27.46	....
15.25	....
(Average 15.9%)	(Average 1.21%)

* The difference between the immune tumor uptakes per gram and the controls is highly significant as evaluated statistically:

Using S. E. of the mean as $\sqrt{\frac{\Sigma dev.^2}{N \times (N-1)}}$ you get the following: Immune 15.9% dose ± 3.87; control 1.21% dose ± 0.316. Solving for t, using

$$V = \frac{(\Sigma dev.^{2(1)}) + (\Sigma dev.^{2(2)})}{N_1 + N_2 - 2}$$

$$\text{S. E. of difference} = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$\text{thus } t = \frac{\text{difference between means}}{\text{S. E. of difference}}$$

then t = in this case to 3.14
From tables P = less than 0.01 which is considered to be a highly significant difference.

The advantages of using large animals like the horse have been pointed out.

From limited experimental evidence not yet reported the author does not believe that specific cancer antibodies *by themselves*, as produced by intraspinal immunization, will be found to exert any detrimental effect on the viability or growth of cancer cells in tumors such as were used. No conclusive evidences of

active or passive immunization effects have been observed to date. It is not believed that cancer antibodies *per se* are antagonistic to cancer cells the way bacterial antibodies are to bacteria. However, by combining a radioactive element with specific cancer antibodies

TABLE V

TRACER EXPERIMENT—INDIVIDUAL READINGS FOR UPTAKE BY REPRESENTATIVE NORMAL TISSUES IN MICE BEARING SARCOMA 180 TUMORS FOUR HOURS AFTER INTRAVENOUS INJECTION OF I-131–TAGGED ANTISARCOMA 180 IMMUNE AND CONTROL HORSE CEREBROSPINAL FLUIDS

Per cent of Dose per Gram Wet Weight of Normal Mouse Tissue (in Paris Mice Bearing Sarcoma 180)

Immune Spinal Fluid No. 7 (10 *Animals Tested*)

Kidney	5.5	7.1	6.9	9.1	9.1	4.2	4.1	6.9	11.0	4.0
Spleen	3.1	3.3	4.1	10.8	7.2	4.2	4.8	5.4	15.0	5.5
Liver	1.4	1.2	2.2	3.1	2.4	1.9	2.6	2.6	2.4	1.6
Muscle and bone	2.2	3.8	2.4	5.4	5.2	2.4	2.0	1.6	4.2	1.9

Control Normal Spinal Fluid (7 *Animals Tested*)

Kidney	5.6	8.7	6.1	7.0	4.3	6.4	6.8
Spleen	22.4	37.3	19.7	11.0	9.0	23.6	25.3
Liver	8.3	15.2	10.6	9.1	6.3	13.2	6.4
Muscle and bone	2.4	3.8	2.3	2.5	1.2	3.8	2.8

TABLE VI

TRACER EXPERIMENT—INDIVIDUAL READINGS FOR UPTAKE BY SPONTANEOUS TUMORS (CARCINOMA) IN SWISS MICE FOUR HOURS AFTER INTRAVENOUS INJECTION OF I-131–TAGGED ANTISARCOMA 180 IMMUNE AND CONTROL HORSE CEREBROSPINAL FLUIDS

Per cent of Dose per Gram Wet Weight of Tumor (Spontaneous, Carcinoma)

Immune Spinal Fluid No. 7	Control Normal Spinal Fluid
2.08	3.43
2.83	0.95
0.55	2.69
0.90	2.28
0.81	1.35
1.75	....
1.07	....
2.30	....
3.63	....
2.23	....
(Average 1.82%)	(Average 2.14%)

produced by the intraspinal route of immunization in large animals, a means of carrying radioactive energy directly and preferentially in the living animal to the same type of tumor tissue used in the preparation of the immune fluid is available.

When human cancer tissue is used in the production of the immune fluid, such combined radioactivity may be expected to have potential diagnostic and therapeutic value. Using various types of human cancer resected at primary operations (these tumors may be frozen solid until prepared for immunization in horses), a stock-pile of corresponding types of cancer antibodies may become available for human application.

The method of intraspinal immunization described may be of value (by using specifically infected tissue, particularly virus-infected cells) in the production of specific vaccines for the diagnosis and treatment of diseases like encephalitis, rabies, distemper, influenza and poliomyelitis. For example, the intraspinal immunization of horses with kidney cells infected with poliomyelitis virus, or the use of attenuated poliomyelitis virus alone, should prove a practical means of obtaining large quantities of *poliomyelitis antibodies* from the cerebrospinal fluid of the animals immunized. These antibodies could then be used for passive immunization and for the treatment of the acute disease in man.

The entire field of intraspinal immunization in large animals is worthy of further exploration.

SUMMARY

1. Heterologous antibodies to mouse sarcoma 180 were recovered from the cerebrospinal fluid of horses immunized by repeated intraspinal (cisterna magna) injections of suspensions of this tumor.

2. Complement fixation tests on the cerebrospinal fluid of such immunized horses revealed positive fixation for sarcoma 180 tumor over and above normal mouse heart and connective tissue.

3. Tracer experiments using radioactive I-131 combined with this immune cerebrospinal fluid showed a preferential localization in the sarcoma 180 tumors in living mice. No such localization was found in spontaneous tumors of other types (carcinoma) in living mice, or in lymphosarcoma in rats.

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Surgical Aspects of Jaundice

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JAUNDICE is a manifestation of a variety of pathologic disorders of the liver and biliary tract. It is characterized by the deposition of bile pigments, chiefly bilirubin, in the tissues of the body. The familiar yellow color of jaundice is due to the increased concentration of bile pigments in the blood. This color is first seen in the sclera, conjunctiva, mucous membranes and the skin. Occasionally a green color predominates because of biliverdin. When jaundice occurs, it is evident that the bile pigments and other constituents of bile are accumulating in the blood.

TABLE I
APPROXIMATE COMPOSITION OF HUMAN BILE

	Hepatic Bile	Bladder Bile
Water	97.49	85.92
Solids	2.52	14.08
Specific gravity	1.010	1.040
Bile acids	0.93	9.14
Mucin and pigments	0.53	2.98
Cholesterol	0.06	0.26
Fatty acids and fat	0.14	0.32
Inorganic salts	0.84	0.65

The polygonal cells of the liver form the bile which then passes into the spaces of bile canaliculi between these cells and into the bile duct system. It may be stored in the liver or in the gallbladder, or pass directly into the duodenum. From 500 to 1,000 cc. of bile are formed daily. Bile is usually golden yellow; as it comes through the liver it has a pH of 7.4 to 8.5. According to Bodansky, it contains bile acids, pigments, mucin, cholesterol and various other lipoids and inorganic salts. Table I shows the different percentages and the composition of human bile.

It is interesting to note the composition of mixed or combination gallstones.[2] (Table II.)

It is thought 1.5 mg. of bilirubin per 100 cc. must be present in the blood before noticeable discoloration of the tissues takes place.

Bilirubin is formed from the hemoglobin, and Mann[3] has shown it continues to be formed even after the removal of the liver and other intra-abdominal organs. Thus, there must be an extrahepatic formation of bilirubin. McNee[18] and Aschoff[4] believe the reticuloendothelial system is involved in this formation.

TABLE II
COMPOSITION OF MIXED OR COMBINATION GALLSTONES

	Per cent
Cholesterol	94.00
Pigment	3.26
Calcium	1.09
Carbonic acid anhydride	1.06
Phosphoric acid anhydride	0.40
Magnesium	0.13
Sodium and potassium	0.05
Fatty acids	Trace

There are three ways in which an increased concentration of bilirubin in the blood may occur. Bodansky's classification is as follows: (1) Hemolytic jaundice: Excessive destruction of hemoglobin supplying a much greater amount of material for formation of bilirubin. If the liver is unable to take care of this excessive load of pigment and can not excrete it rapidly into the bile passages, bilirubin accumulates in the serum and the concentration of bilirubin rises. (2) Toxic jaundice: This type is due to damage to the liver parenchyma, especially the polygonal cells. The specific causes are infections, toxic reactions or occasionally mechanical defects. Thus, the extraction of bile does not take place and the concentration of bilirubin in the serum rises. The new drug, thorazine, has produced at least four to six cases of jaundice in Portland. (3) Obstructive jaundice (or regurgitation jaundice[5]): This type of jaundice is produced by obstruction or impediment to the flow of bile. The impediment

may be located any place from the bile canaliculus to the ampulla of Vater. The bile capillaries are dilated and may even be disrupted by the back pressure. The bile flows into the perilobular lymphatics and then into the blood stream, resulting in jaundice.

DIFFERENTIAL DIAGNOSIS OF JAUNDICE

Patients with jaundice can be classified as to severity of diagnostic possibilities into three groups.

In 60 to 70 per cent of cases, the diagnosis can be made accurately from the history, physical and x-ray findings, and with perhaps the additional help of the direct and indirect van den Bergh test, urobilin and urobilinogen.

In 15 to 25 per cent of cases the diagnosis can be made by the following liver function tests: cholesterol flocculation and serum phosphatase concentration. These two tests are insufficient in 5 to 10 per cent of cases. All the tests must be used in order to obtain the diagnosis; some will remain in doubt until surgery is performed or a liver biopsy is taken. Two main groups are cholangiolitic hepatitis and posthepatic obstruction with secondary hepatic injury. The etiology is ascending infection or long-standing jaundice, or both.

The parenchymatous function of the liver is not impaired in obstructive liver disease unless it is of very long standing. Therefore, the following tests should be performed: thymol turbidity, cephalin-cholesterol flocculation, bromsulphalein retention, albumin-globulin ratio and percentage of free cholesterol within normal limits.

Table III lists results of tests helpful in differentiating surgical and medical jaundice.

Table III illustrates classic cases and is valuable because the majority of cases can be diagnosed by those tests alone. The alkaline phosphatase usually parallels the serum bilirubin and the jaundice of obstruction is almost always more marked than medical jaundice. If the phosphatase falls and the bilirubin does not, death can be expected. In extrahepatic biliary obstruction there is no liver damage for some time. Thus, the cephalin flocculation and the thymol turbidity tests are normal in early obstructive jaundice. If these tests give positive results early, the case is probably one of hepatitis. However, one must not forget that 10 to 15 per cent of cases of hepatitis are periportal hepatitis and cholangitis, and the tests will give negative results. In patients with medical jaundice due to hemolysis, stones and obstruction may also develop.

SYMPTOMS

The symptoms of biliary colic, chills and fever, especially with intermittent jaundice, is usually an indication that a benign lesion is present. The most common cause for the aforementioned symptoms is a common duct stone. These symptoms, especially nausea and vomiting, will often occur after the patient has eaten a meal.

TABLE III
LIVER FUNCTION TESTS

Tests	Surgical	Medical
Van den Bergh	Direct	Indirect
Urinary urobilinogen	Absent	Increased
Fecal urobilin	Usually absent	Increased
Serum alkaline phosphatase	Usually >15 B.U.	5 to 10 B.U.
Cholesterol	>300 mg./100 cc.	Normal (150 to 200 mg.)
Serum proteins	Normal	Decreased
Cephalin flocculation	Negative	Positive

Probably the most important indication of obstructive jaundice is clay-colored stools. Progressive jaundice, especially if painless with acholic stools in a patient over forty years of age, is usually due to malignancy. In 80 per cent of cases the malignancy is in the head of the pancreas; the gallbladder will be enlarged and frequently definitely palpable.

Surgical aspects of regurgitation or obstructive jaundice arise from obstruction of the common bile duct. If the duct is obstructed by a mucous plug or a stone, surgical relief is quite easy. However, when a stricture or a malignancy has developed, the difficulties increase.

In 1954, a five-year study was made of cases of common duct obstructions and injuries at Good Samaritan Hospital. Common bile duct obstruction due to stones in this series was 33 per cent. There were four injuries to the common duct. While injury to the common duct may occur during operative procedures in acute and subacute cholecystectomy, most of these injuries occur in relatively simple operations on the biliary tract. They are most always the result of careless and faulty surgery.

OBSTRUCTIVE OR SURGICAL JAUNDICE

Recently strides have been made in diagnosis by the use of cholografin.® It is used intra-

venously usually after the gallbladder has been removed, and is very effective in outlining the common duct, common hepatic duct, right and left hepatic ducts, and intraductal system. It also frequently shows a long cystic duct or a remnant of gallbladder which may contain stones.

The use of this dye will lower the incidence of reoperation. It will conversely frequently show a stone; therefore, the need for reoperation. Cholografin appears to be a safe drug which will help evaluate the postcholecystectomy syndrome. It not only will help determine the presence or absence of intraductal calculi but also will help determine ductal obstruction from tumor, stricture or other sources such as spasm or hypertrophy of the sphincter of Oddi.

Oral cholecystography is usually adequate for the examination of the gallbladder, but at times the intravenous substitution of cholografin is valuable. It provides positive evidence that the right amount of dye has entered the blood stream. It cannot be used when there has been serious liver damage. Careful radiographic technical safeguards must be instituted to obtain a concise picture.

Bell reported 1,414 cases of biliary tract disease operated upon from 1930 to 1954. Exploration of the common duct was carried out in only 19 per cent. Common duct stones were found in 52 per cent of the common ducts explored, or 10 per cent of the entire series. He believes that each case should be considered individually; too many common ducts are needlessly explored.

Often frequent and unnecessary exploration of the common bile duct results in injury and permanent harm.

Stones. Most common duct stones arise from the gallbladder and are passed through the cystic duct into the common duct. Hicken[8] believes 7 per cent arise from the liver itself. Many times stones in the common duct are silent. Sooner or later they manifest themselves by producing a ball valve obstruction type of jaundice or by becoming firmly lodged in the ampulla of Vater. If the stone is firmly fixed in the ampulla, the icterus index rises steadily and the direct van den Bergh test gives a positive result. In order to relieve the condition it is necessary to remove the gallbladder, open the common duct and remove the stone or stones. These are the usual indications for exploration.

Frequently the overlooked stone in the common duct will produce jaundice weeks and even years later. This can be avoided by cholangiography. (Table IV.) Diodrast® can be injected through the cystic duct into the common duct pointing the needle up toward the liver to obtain a good flow of dye into the intraductal system. If there are any stones present, they can readily be seen. The duct can then be opened. Conversely, if the duct is clear, surgery with its inevitable trauma is obviated.

TABLE IV
TYPES OF CHOLANGIOGRAPHY

I. Operative
  A. Immediate
    1. Cystic duct injection
       Diodrast injected into cystic duct
    2. Spasm in distal portion of common duct
    3. Common duct injection
       Stone in distal portion of common duct
    4. Retrograde (opened ampulla)
  B. Completion (control)
    1. Dye injected through T-tube
II. Postoperative (secondary)
    Clear postoperative cholangiogram with T-tube
    Pancreatic duct shown

Early cholecystectomy should be advised before stones have dropped into the common bile duct or have perforated into the duodenum or transverse colon. Baker[9] has found it inadvisable to explore a common bile duct with a diameter less than 10 mm. When the common duct is explored it is well to pass scoops both proximally as well as distally. There may be stones in the common hepatic duct or in the right or left hepatic ducts. A Bakes dilator or a curved uterine probe should always be passed through the ampulla of Vater into the duodenum. It is advisable to dilate the opening gently, if at all, as pancreatitis has followed forceful dilatations. Before the T-tube is placed in the common duct and the duct is closed, the duct should always be irrigated thoroughly with saline. Small stones or gravel will remain unless the duct is washed out.

Stricture of the Common Duct. Strictures are almost entirely due to operative trauma. They must be relieved, if the patient is jaundiced, by excising the stricture and performing end-to-end anastomosis. If possible, it is wise to bring the T-tube out through another opening, either above or below the suture line. If it is impossible to repair the stricture, choledochoduodenostomy or a Roux-Y type of opera-

TABLE V

CARCINOMA OF VARIOUS PARTS OF BILIARY SYSTEM

Source	Common Bile Duct	Junction of Cystic Ducts	Junction of Common Hepatic Ducts	Common Hepatic Ducts	Cystic Ducts	Right and Left Hepatic Ducts	Gall-bladder	Total
Good Samaritan Hospital....	2 in ampulla of Vater	..	..	..	2	..	18	22
Rolleston and McNee.....	34	2	28	19	6	4	..	91
Stewart.....	..	..	..	..	27	..	..	27
Milles.....	..	..	..	..	37	..	..	37
Cooper.....	..	..	..	..	..	..	21	21

tion should be performed, suturing the proximal end of the common duct into the jejunum.

Inflammation. The most worthy example of inflammation of the extrahepatic bile ducts is exemplified by the condition known as diffuse stenosis. This condition manifests itself at first in one particular part of the extrahepatic system. Soon it extends and may involve the entire ductal system.

Judd,[10] Cattell[11] and Carter[12] have reported thirty-nine cases of cholangitis. Roberts[13] recently reported two cases and discussed this condition under "stenosing cholangitis."

These patients' attacks simulate acute cholecystitis. Surgery reveals that the gallbladder is normal and the common bile duct is small, edematous and resembles a hard tube with a very small lumen present. These patients gradually become jaundiced; as time goes on their condition becomes worse and death results.

It is difficult to know what sets up the inflammation in the liver and the ductal system which gradually produces almost complete stenosis. This condition may be controlled with the new antibiotics, thus preventing progression.

Mucous Plug. Mucous plugs and debris may be present in the common bile duct and can be removed at surgery by passing scoops and washing out the duct. The common duct should then be x-rayed through the T-tube. By so doing, one can be sure there is no obstruction in the distal portion of the common duct.

If debris collects while the T-tube is still in place following surgery, this can be washed out through the T-tube.

Neoplasms. Benign neoplasms: Benign neoplasms are usually fibromas which occur at the ampulla of Vater. This condition can be relieved by resecting the distal end of the common duct and then reimplanting it into the duodenum.

Malignant neoplasms: Obstructive jaundice may be produced by a malignancy occurring in the head of the pancreas. This occasionally may be relieved by a Whipple operation in favorable cases but generally the carcinoma has progressed so far a side-tracting operation may be necessary. This may be accomplished by anastomosis between the gallbladder and the duodenum or the jejunum.

In 1953 at the Mayo Clinic 1,647 operations were performed on the gallbladder; only eight Whipple operations could be performed. There were six malignancies of the ampulla of Vater and two of the head of the pancreas.

Carcinoma of the gallbladder and bile ducts is a serious and difficult problem to handle. In 1952, a ten-year study of our cases revealed that 540 operations were performed on the gallbladder, including twenty-two cases of carcinoma of the gallbladder and bile ducts. (Table v.)

Carcinoma of the gallbladder is thought to occur in patients who have had a long history of gallstones. Table VI shows the incidence of gallstones in carcinoma of the gallbladder.

The second condition which is thought to be precancerous is papilloma of the gallbladder. This elusive condition is reported in various

clinics throughout the country in variable percentages. At the Mayo Clinic from 1893 to 1937 29,701 gallbladder operations were performed, revealing 2,754 cases of papilloma of the gallbladder. Kerr and Lendrum[16] found only eleven cases acceptable to fulfill their requirements for a papilloma of the gallbladder. The confusion no doubt arises from the fact that the Mayo Clinic uses different criteria than Kerr and Lendrum. Kerr believes it should be a definite tumor with branching of the papilloma. Most authorities agree that papilloma of the gallbladder occurs once in every 100 gallbladder operations.

TABLE VI
INCIDENCE OF GALLSTONES IN CARCINOMA OF THE GALLBLADDER

Source	No. of Cases	Incidence (%)
Good Samaritan Hospital	22	86.4
Massachusetts General Hospital	50	88.0
Sternberg	115	78.3
Finsterer	46	93.5
Judd and Gray	212	64.6
Illingworth	38	81.5
Cooper	48	79.0

Phillips[17] found only one instance of carcinoma of the gallbladder occurring in papillomas in 500 gallbladder operations. More recently, McNee reported four cases of carcinoma occurring in papillomas at Memorial Hospital. It may well be a precancerous condition. If this condition is discovered by x-ray, the gallbladder should be removed.

Obstruction of the bile flow may be produced by compression on the common duct by enlarged lymph nodes. These lymph nodes at times surround and completely compress the outlet of the common duct.

The only prophylactic treatment known is removal of the calculous and papillomatous gallbladders. In three of our cases when the gallbladder with stones was removed, concurrent carcinoma of the gallbladder was noted. These carcinomas were small and it is believed that the patients will be well.

TREATMENT OF SURGICAL JAUNDICE

Treatment depends upon early and accurate diagnosis. The new methods at our disposal such as the new gallbladder dye, cholografin, which will frequently outline not only the gallbladder but also the common duct itself, increases the accuracy of correct diagnosis. Cholangiography during operative procedures will tell us whether there are stones present in the common duct before it is opened. After the duct has been opened and stones removed, operative cholangiograms through the T-tube will confirm whether the duct is clear. Operative cholangiography will frequently help us to diagnose anomalies of the common bile duct and the duodenum. Through the use of operative cholangiograms the common duct has been observed to enter into a diverticulum of the duodenum instead of the duodenum itself.

Recently Clark made a survey of eighty-seven surgeons who used cholangiograms. He found that more surgeons than ever before were using operative and postoperative cholangiograms. If operative cholangiograms are properly employed, secondary operations of the common duct can almost be eliminated. Hutchinson reported obtaining a correct diagnosis in 80 per cent of his cholangiograms.

With proper use of operative cholangiograms injury to the common duct may well be avoided. This tragedy should be avoided and every procedure which will help prevent needless injury to the common duct should be carried out.

A cholangiogram of the common duct may be done to see if residual stones or debris remain. In this manner one is able to help avoid injury to the common bile duct.

SUMMARY

1. Jaundice has been discussed mainly from the surgical aspects. The formation of bile, its composition and the composition of gallstones have been reviewed.

2. The classification of jaundice with discussion of some of its various phases has been recorded, especially its surgical divisions.

3. The different surgical causes of jaundice have been emphasized.

4. Reoperation on patients with common duct stones can be markedly reduced, if not avoided, by operative cholangiograms. Completion cholangiograms just before the abdomen is closed are especially valuable.

5. Preoperative preparation with vitamin K, antibiotics and blood transfusions have widened the scope of surgery. After final preparation has been made and the diagnosis is established,

more radical surgical procedures can be carried out. Before the advent of our modern preparations many patients were lost who now can be saved.

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Precision-Formed Polyethylene Implants for Correction of Mandibular Contour

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THIS paper describes a method to form precision polyethylene implants to correct mandibular contour and reveals successful results achieved in twenty cases during the past fifteen months. These polyethylene implants were used in cases of microgenia, without malocclusion, as a supplement to other surgical procedures intended to bring the mandible forward, and in certain cases of micrognathia with malocclusion in which surgical advancement of the mandible was not indicated because of the nature of the malocclusion and deformity. In all these conditions the implants not only restored normal contour but also increased the support of the advanced soft tissues over the mandible. This enabled the lips to meet more easily, and as a result speech was improved and mouth-breathing reduced.

Although many defects of the face and skull are best repaired with bone or cartilage, these biologic materials often produce indifferent results in some of these deformities. For example, in the past, mandibular contour deformities were corrected by onlay grafts of cartilage or bone. These grafts, however, have since been found to suffer from serious deficiencies. Preserved cartilage, for instance, fails to become fully immobilized and is often absorbed. Autogenous cartilage tends to curl after it is transplanted. Moreover, the donor area causes the patient considerable pain and disability.

In like manner, autogenous bone suffers from disadvantages which have led to its discontinuance for mandibular onlay grafts. One of these disadvantages is that removal of the bone from the ilium results in considerable morbidity. Although many authors tend to minimize the importance of this effect, a patient who cannot walk for ten to fourteen days after removal of a full-thickness section of his ilium is not likely to share this view. Even small grafts taken from the ilium create postoperative discomfort out of proportion to the contour defect that is being repaired.

Another inherent fault of autogenous bone is evidenced by the fact that some grafts of this material which were inserted by the author four to five years ago have shown a small but noticeable decrease in size due to absorption. This clinical finding, which is supported by the reports of other investigators,[1] should not be surprising since it has long been known that bone responds like muscle to physiologic stress and will be absorbed when it fails to serve a physiologic need. Controversy still exists regarding the permanence of this type of graft; however, it seems probable that in time a considerable number of autogenous onlay bone grafts will share the fate of preserved cartilage implants. The final reason for discontinuing autogenous bone onlay grafts is the waste of time and bone involved in the shaping of the outside and inside surfaces of the graft at the operating table.

In view of these difficulties with bone and cartilage, attention has been focused from time to time on plastic substitutes. Among the more promising of the newer plastics is polyethylene, which was first used in neurosurgery by Ingraham, Alexander and Matson,[2] and in plastic surgery by Rubin, Robertson and Shapiro.[3] However, like the biologic materials, polyethylene had to be shaped at the operating table under very adverse conditions. When the polyethylene was finally inserted, it demonstrated the same mechanical disadvantages that frequently were encountered with the biologic materials (rocking, displacement, dead space, obliteration of the gingivolabial fold and poor continuity of the margins of the graft

with the surface of the mandible). How these disadvantages were finally overcome will be described fully in this report.

POLYETHYLENE

The properties of polyethylene have been covered in detail by other investigators. This plastic substance meets the essential requirements, as listed by Clarke et al.,[4] of a synthetic material that can be used for implants. Especially desirable is polyethylene's thermoplastic property which enables the operator to shape the material to any desired form by compression or injection-molding.

Reports by a number of investigators indicate that chemically pure polyethylene is noncarcinogenic. In the work of Rubin[5] and Clarke et al.[4] polyethylene implants were buried in humans and in laboratory animals for periods up to three years. After microscopic examination of biopsies, they found that the cellular and vascular response to the implant was nil. Gordon[6] adds that to date there has not been a single recorded instance of malignancy developing in a human being as a result of a plastic having been buried in the tissue. Gordon's observation is significant in view of the countless numbers of nylon sutures buried in humans during the past two decades.

CONSTRUCTION OF MANDIBULAR PRECISION POLYETHYLENE IMPLANTS

Exposure of Mandible. The patient is seated in a chair equipped with a head rest. Using local anesthesia, the operator incises the interdental papillas from first molar to first molar. Bilateral vertical incisions are made through the gingival mucosa from the interproximal space in front of the first molars to the inferior border of the mandible. With a periosteal elevator, the soft tissues, including the periosteum, overlying the mandible between the vertical incisions, are reflected downward from the gingival margin until the inferior border of the mandible is freely exposed. In the process the mental neurovascular bundles are also easily exposed. They are dissected so that they will lie flat against the mandible when the impression is taken. (Fig. 1.)

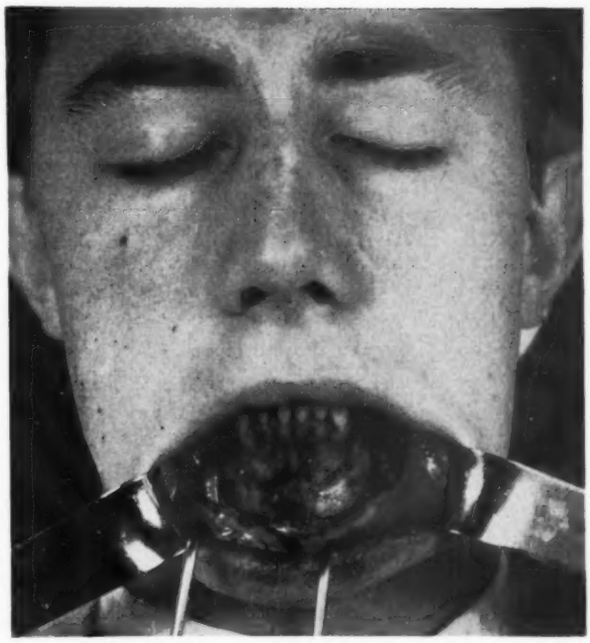


FIG. 1. Exposure of anterior surface of mandible and neurovascular bundles.

Negative Impression. An impression of the exposed mandible is made with Kerr's impression compound, a dental material used for taking impressions of the soft and hard tissues of the mouth. (Literature describing the physical and working properties of this material can be obtained from any dental supply house.) After the impression is taken, the mucosa is tacked back into place with several sutures and a compression dressing is applied to the chin for twenty-four hours.

Positive Impression. The positive impression, or cast, of the mandible is obtained by filling the negative with dental stone. This cast is retained for reference; a duplicate cast is made for working purposes. (Fig. 2A and B). On the duplicate cast the mental neurovascular bundles, which extend from the mental foramen to the inferior border of the mandible, are trimmed away. (A sectional impression extending under the mental nerves obviates the need for this trimming and increases the accuracy of the cast.)

Wax Model. Using dental wax, the operator now sculptures a model of the desired implant on the cast. (Fig. 2C.) Feathered extensions above and below the mental nerve will not only establish the continuity of the margins of the implant to the surface of the mandible but also will enhance retention of the implant. Cephalometric x-rays and tracings should be made as they are very important in determining the shape and dimensions of the model.

Formation of Implant. The wax model is invested in dental stone. The two halves of the

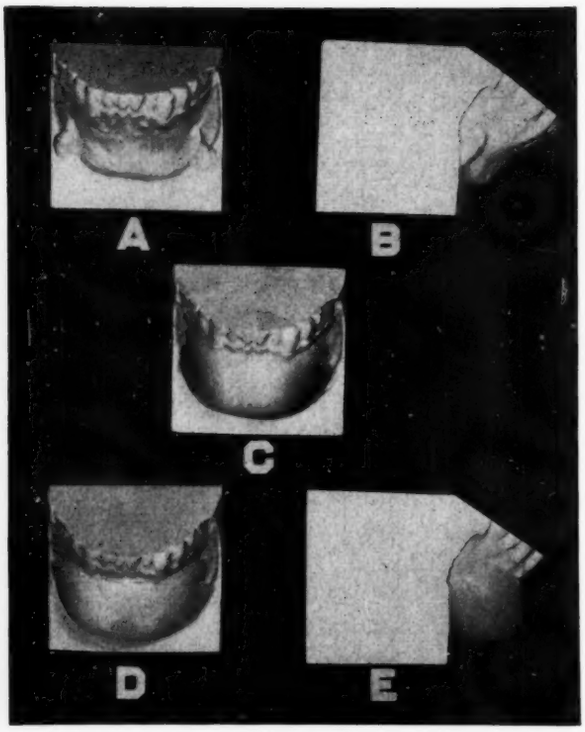


FIG. 2. A and B, positive impressions or casts of mandible oriented by cephalometric x-rays. C, wax model of implant. D and E, polyethylene implants.

mold are separated and the wax is removed. The implant may then be formed either by compression or injection-molding. When the implant is compression-molded, the empty mold is filled with polyethylene granules and the implant is formed by the application of heat and pressure. This method is satisfactory with small implants; but because it produces air bubble defects in large implants, it has been abandoned in favor of the injection method which uniformly gives a smooth, satisfactory replica of the wax model. In the injection method a 3/8 inch hole is drilled from the top of the investing flask to the mold, and the molten polyethylene is then forced through this sprue into the mold. The polyethylene should be heated to 300°F. before injection but the mold should remain at room temperature. After the formed implant is recovered, it is trimmed and multiple holes are drilled to permit connective tissue ingrowth which will provide additional fixation of the implant to the mandible. (Fig. 2D and E.)

Insertion of Implant. The insertion of the implant is delayed one month to permit firm healing of the gingiva to the cervical margins of the teeth. Through a submandibular incision the soft tissues, including the periosteum, are elevated. The mental neurovascular bundles are exposed. It may be necessary to make a vertical midline incision through the relatively inelastic band-like periosteum to prevent it from pulling the soft tissues upward and thus creating a double chin effect. The implant is now inserted so that the lateral extensions of one end embrace the mental nerve and the entire implant is carried slightly laterally. The other end is elevated and the implant is brought back to the midline where it should seat firmly. The subcutaneous tissues are closed with fine chromic catgut, and the skin is closed with fine silk suture. An elastoplast compressive dressing is applied for several days.

COMMENT

At first glance the construction of precision implants that require impressions, casts, models and molds may seem involved. Actually the procedure is very simple, even for an operator inexperienced in the use of dental materials. There are three steps: (1) secure the impression; (2) sculpture the wax; and (3) insert the implant.

Most dental laboratories are equipped with an injection-molding machine, and for a nominal charge will construct the casts, invest the wax model and inject the polyethylene.

ADVANTAGES OF MANDIBULAR PRECISION-FORMED POLYETHYLENE IMPLANTS

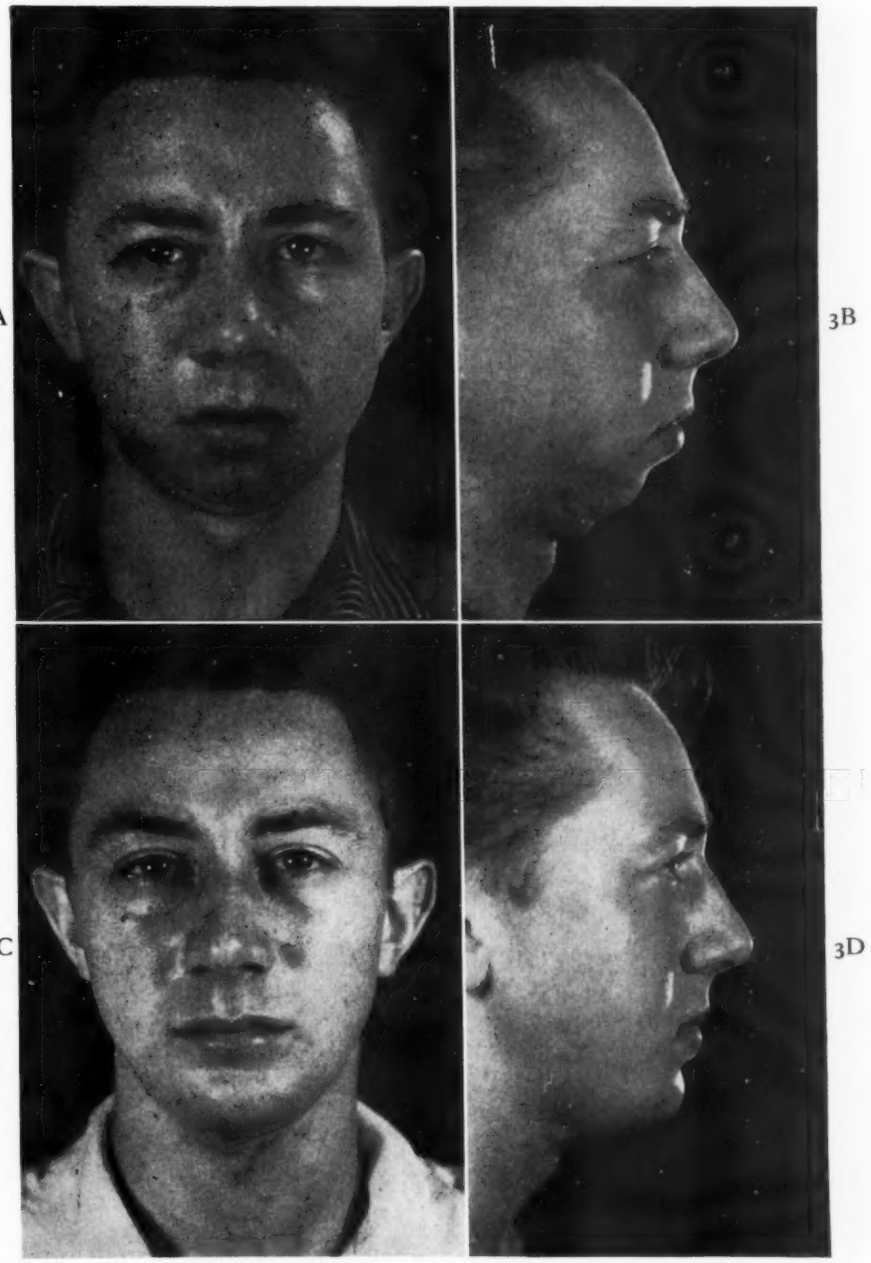
Precision-formed polyethylene has been found to be the method and material of choice for mandibular implants for the following reasons:

1. Intraoral exposure of the symphysis and mental areas of the mandible for the impression is a brief office procedure. The slight to moderate postoperative edema, lasting twenty-four to thirty-six hours, does not interfere with the patient's routine activity.

2. The operating time is reduced to a minimum since the implant is constructed in the laboratory instead of in the operating room, as is the case with autogenous grafts.

3. The wax model may be leisurely sculptured in any shape or design.

4. Contact between the inner surface of the implant and the outer surface of the mandible is intimate and precise. This results in: (1)



3A 3B 3C 3D

FIG. 3. Micrognathia with malocclusion despite prolonged orthodontic treatment. Surgical advancement of mandible not indicated because of nature of malocclusion and deformity. Mandibular contour corrected with precision polyethylene implant. A and B, preoperative front and profile views. C and D, postoperative results.

absence of infection-producing dead space and serum; and (2) firm seating, so that even on the laboratory cast the implant is difficult to dislodge by any forward, vertical or lateral force.

5. The margins of the implant are feathered so that most patients cannot detect by palpation where the implant ends and the mandible begins. Many patients volunteered the statement: "The chin feels like my own"; by way of contrast, autogenous grafts often feel to the patient like an afterthought of nature.

6. The gingivobuccal and gingivolabial folds are preserved because the feathered margin of the polyethylene implant extends upward

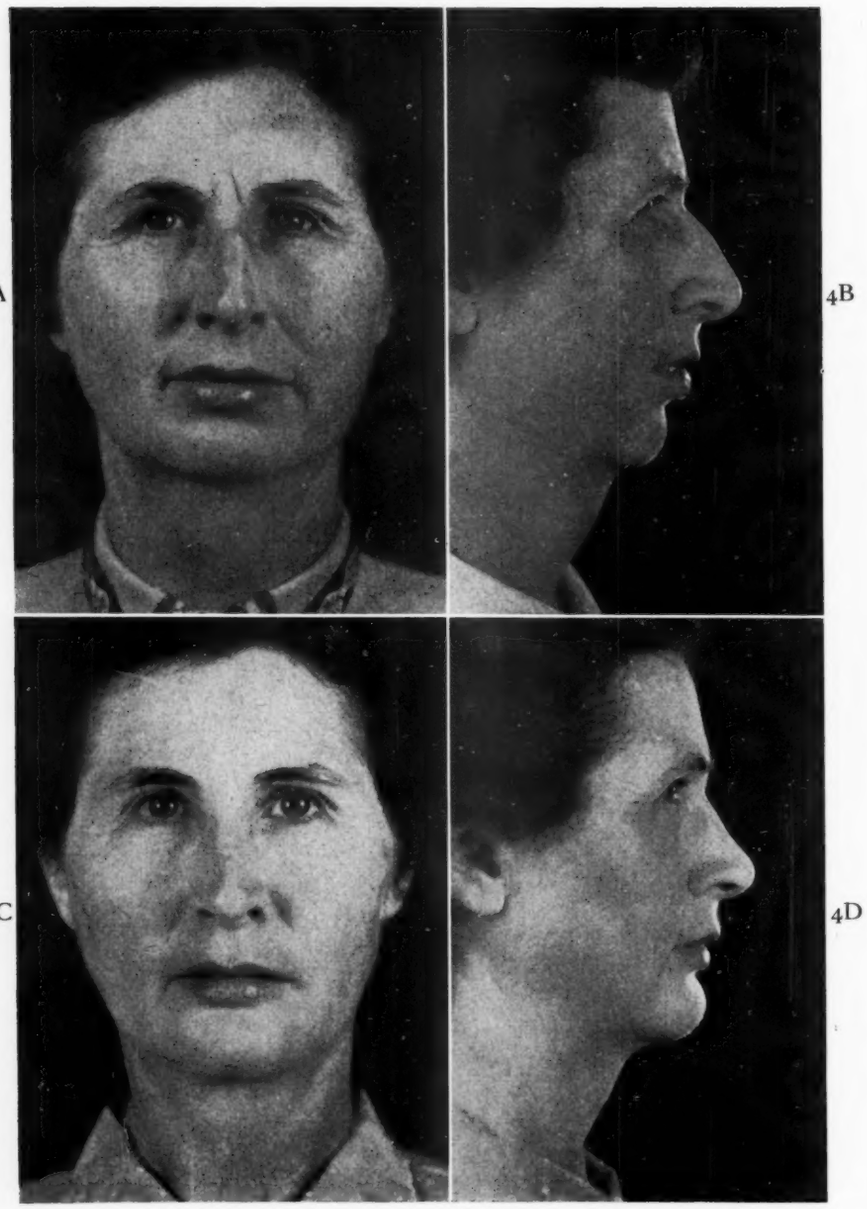


FIG. 4. A and B, preoperative front and profile views of mandibular contour defect. C and D, postoperative views of defect corrected with precision polyethylene implant. Rhinoplasty enhanced final result.

under the gingival mucosa instead of displacing it, as frequently occurs with large onlay grafts.

7. In the rare case of infection the implant is easily removed and reinserted at a later date.

8. In this method there is little danger of entering the oral cavity while preparing the bed for the reception of the implant. Since the operator may easily measure the vertical distance from the inferior margin of the mandible to the gingival margin on the cast or implant, he can locate the tip of his periosteal elevator at all times.

RESULTS

During the past fifteen months, precision-formed polyethylene mandibular implants have been used in twenty cases, with gratifying results. Figures 3 to 5 show typical results in three unselected cases.

Only two complications occurred in this

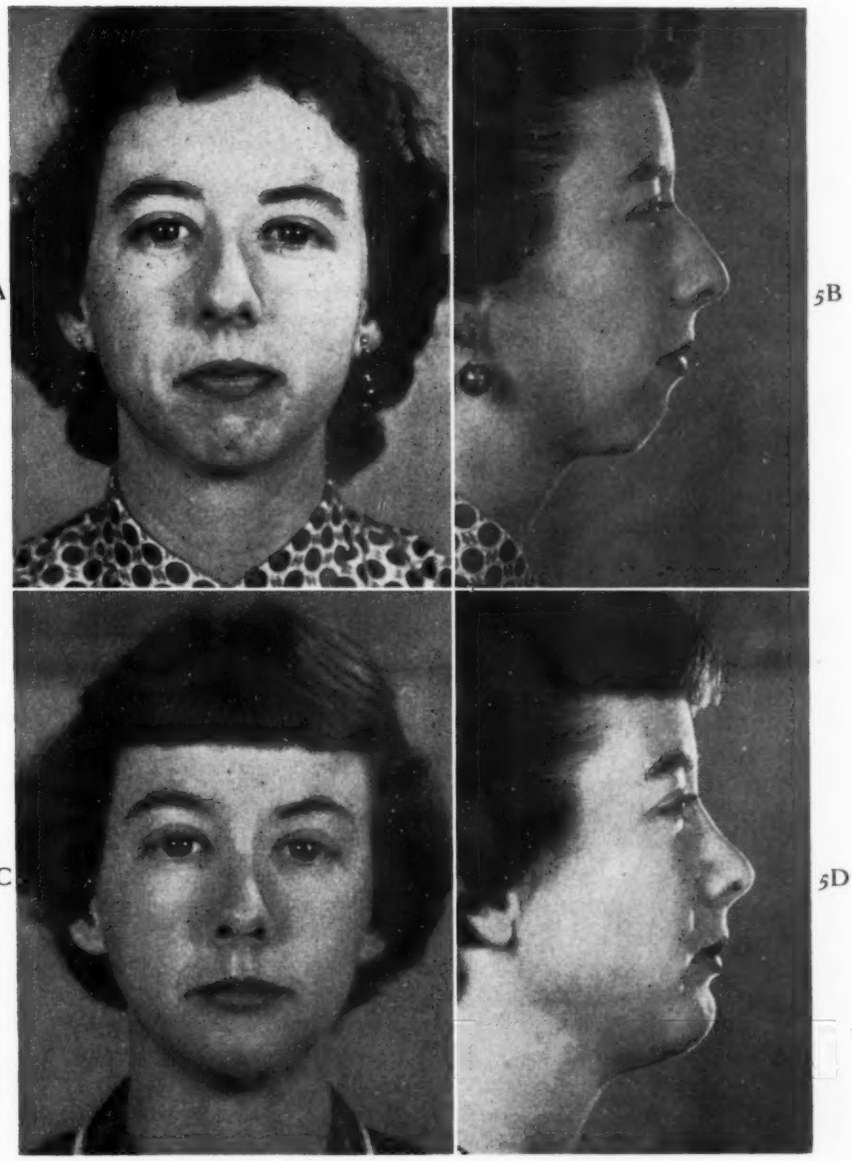


FIG. 5. A and B, preoperative front and profile views of mandibular contour defect. C and D, postoperative views of defect corrected with precision polyethylene implant. Rhinoplasty enhanced final result.

series of twenty cases. In one case a postoperative infection forced the removal of the implant, but the implant was successfully reinserted after the infection subsided.

In the second case the operator overextended the inferior margin of the implant. The submandibular incision was reopened several months later and the excess polyethylene was easily removed with a scalpel. At this time it was observed that the implant was enclosed in a smooth, thin envelope of fibrous tissue with columns of connective tissue growing through the drill holes. The implant was fixed so firmly that it could have been removed only with considerable difficulty.

SUMMARY AND CONCLUSIONS

Because of increasing dissatisfaction with the unpredictable behavior of biologic grafts, as well as with the morbidity caused by the donor site, a simple method has been developed to form precision polyethylene implants.

These implants can be constructed in any desired shape. When introduced with strict sterile technic, they are received kindly by the tissues, with little or no reaction. They will seat firmly and resist displacement. Detection of the implant by palpation is difficult.

Precision-formed polyethylene implants were used during the past fifteen months to correct mandibular contour in twenty cases of microgenia and micrognathia. The results to date have been far superior to those of former cases in which the same defect was corrected with autogenous iliac bone and cartilage as well as preserved cartilage.

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The best therapy for rectal prolapse is a suitable operation, but occasionally the patient is too elderly or weak or refuses radical surgery. In these latter instances perirectal injections of a sclerosing solution will give satisfactory results. Maintenance of a tube in the rectum is part of the technic. It might be well to attempt treatment of some cases of rectal prolapse by the injection method; if a time comes when we are temporarily without hospital facilities because of fire, etc., we will be very glad that we acquired some experience with the injection treatment of these and similar lesions. (*Richard A. Leonardo, M.D.*)

Intussusception Due to Invaginated Meckel's Diverticulum

PRESENTATION OF TWO CASES AND AN ANALYSIS OF FIFTY-TWO CASES COLLECTED FROM THE LITERATURE

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INTUSSUSCEPTION is of interest to the surgeon since it presents him with an acutely ill patient with a pathologic process which can be corrected by surgical means. Most intussusceptions are seen in infants under two years of age and in these cases, too frequently, an etiologic factor cannot be demonstrated. This paper deals with a specific cause of intussusception, namely, invaginated Meckel's diverticulum. We studied all the cases indexed as intussusception at Henry Ford Hospital and found a total of seventy, only two of which were due to invaginated Meckel's diverticulum.

Thus, from 1918 until 1952 approximately 700,000 patients were seen in the Henry Ford Hospital and Clinics. Seventy cases of intussusception were proved by x-ray or operation; only two were due to invaginated Meckel's diverticulum.

Since the lesion is so uncommon and no individual can amass a large series, we believed that an analysis of cases reported in the literature and the report of our two cases would be of interest. The last extensive review of this subject was reported by Harkins in 1933.[1] He was able to collect 160 cases. The present study can be considered as a sequel to that work. Other valuable reviews of this subject in the past were those of Lower,[2] Hertzler and Gibson,[3] and Gray.[4]

According to Kittle,[5] early observations of this diverticulum were made by Fabricus Hildanus in 1598, Lavater in 1672, Littre in 1700 and Bose in 1799, among others. The lesion is appropriately named after Johann Frederic Meckel who fully appreciated the nature of this lesion and described it in correct detail in 1809. He accurately pointed out its antimesenteric location in the ileum, its relation to the omphalomesenteric duct and its histologic characteristics.

We now know that in fetal life the intestine and the yolk sac communicate with each other. This communication becomes narrowed and elongated and is known as the vitelline duct. Later it becomes occluded and forms a fibrous cord. Eventually this is absorbed so that there is no attachment of the normal small intestine to the umbilicus. If the vitelline duct persists as a tubular outpouching on the antimesenteric side of the small intestine, the diverticulum named after Meckel occurs. It contains the same histologic structure as the ileum but may also contain gastric, pancreatic or even colonic mucosa.

Meckel's diverticulum is found in approximately 2 per cent of the population. Invagination of this lesion is not common. It is presumed that the intussusception is caused by the peristalsis of the ileum acting on the inverted diverticulum, thus telescoping the ileum upon itself.

The relative incidence of intussusception due to invaginated Meckel's diverticulum, when compared to a large series of intussusception, is of interest. (Table 1.)

Thus only one case of intussusception in fifty (2 per cent) will be due to invaginated Meckel's diverticulum.

Onset of the illness is usually sudden. A previously healthy infant or child is brought to the hospital with severe, colicky, intermittent abdominal pain which causes the infant to cry out. The child may scream with pain

during a seizure but may even fall asleep for a few minutes between seizures. Adults locate the pain in the periumbilical area and a long history of recurring cramping pain of several years' duration may be elicited. Chronicity of symptoms is not at all uncommon in adults.

TABLE 1

Authors	Total Cases of Intussusception (1,122)	Cases Due to Invaginated Meckel's Diverticulum (21)
Walton, 1911 (quoted by Harkins[1])	239	4
Koch and Oerum, 1912 (quoted by Harkins[1])	400	7
Perrin and Lindsey, 1921[6]	400	5
McIver, 1928[7]	13	3
Ponka, 1952	70	2

Vomiting commonly follows the pain. Bowel movements tend to diminish in amount and later the passage of blood and mucus may be seen.

Examination generally reveals an acutely ill infant or child with severe bouts of pain. Early cases show no elevation of temperature or pulse; however, a rise does occur as infection and dehydration develop. An abdominal examination reveals findings of the greatest importance. A palpable, sausage-shaped mass may be discovered along the course of the colon, particularly in the lower right quadrant of the abdomen. At times this mass may reduce spontaneously and confound the observers. In this series an abdominal mass was demonstrated in twenty of forty-nine cases. One should bear in mind that the hepatic and splenic flexures are protected from the examining hand by the costal margins. Masses here can be easily overlooked.

Distention is noted in cases in which obstruction has been present for some time. Tenderness and rigidity suggest the presence of peritonitis.

Rectal examination is most important since either a mass or blood and mucus can be demonstrated in a large proportion of cases. This examination must never be omitted. It is disappointing to find so many patients with no reference to this simple examination which can be extremely informative.

The following two cases of intussusception due to invaginated Meckel's diverticulum were seen at the Henry Ford Hospital.

CASE REPORTS

CASE I. M. J. P., a five month old female infant, had been ill for three days. Vomiting, abdominal pain and an abdominal mass were noted. The child passed bloody mucus. The clinical diagnosis was intussusception.

A transfusion of blood was given and intravenous saline was administered preoperatively. At surgery a mass was found in the pelvis consisting of transverse colon, ascending colon, cecum and terminal ileum. Reduction was performed with ease until the ileum was reached. This was reduced with difficulty and the terminal ileum was found to be gangrenous. The outlook was poor but resection and end-to-end anastomosis were performed.

The child died four hours after surgery despite intravenous fluids and transfusions.

The following report, a most unusual case of intussusception, is the second of its kind I have been able to find. The case described by Clute[18] was similar.

CASE II. S. S., a forty-six year old factory worker, was admitted to another hospital on May 13, 1951, with a history of intermittent abdominal pain of six months' duration. No nausea or vomiting had been noted. Cholecystograms, gastrointestinal films and retrograde pyelograms were within normal limits. The impression was that the patient had subacute catarrhal appendicitis. He was discharged and later readmitted to the same hospital with "the same type of intermittent pain, accompanied by nausea and vomiting." Further x-rays revealed partial obstruction, probably in the lower ileum. The impression at this time was that the patient had ileitis. On May 21, 1951, appendectomy was performed. The pathologist's report was subacute catarrhal appendicitis with obstruction.

We saw this patient for the first time on January 25, 1952. He stated that he felt dizzy that morning while having a cup of coffee at an industrial plant. Subsequently he passed two dark stools and later fainted. He gave a history of having cramping abdominal pain for about two years. The previously described appendectomy had been performed eight months

before without relief of symptoms. Food failed to relieve the cramping abdominal pain. He had been passing black stools from time to time. He vomited once and complained of sweating with episodes of pain.

Physical examination revealed a pale, chronically ill forty-six year old man. A questionable mass was palpated in the right lower quadrant of the abdomen. We describe it thusly for we believe that the mass was palpated by those examining the patient when the intussusception was present. However, other examiners were unable to outline it for the intussusception reduced itself spontaneously for variable periods of time. This view is supported by the long history of recurrent symptoms. Slight tenderness was present, but no rigidity or guarding. No mass was palpated on digital rectal examination. Dark stools were present. The patient was admitted for further study. A bleeding duodenal ulcer and a possible mass in the right lower quadrant of the abdomen were to be investigated.

Significant laboratory data included a hemoglobin of 10 gm., a red blood cell count of 3.5 million and a dark green stool showing a 4 plus guaiac.

While in the hospital he had episodes of cramping abdominal pain which suggested intermittent small bowel obstruction. He improved after Miller-Abbott tube decompression and administration of parenteral fluids.

X-ray studies revealed a normal stomach and colon. The barium enema showed a considerable reflux of barium into the distal ileum and a filling defect, not unlike intussusception, was observed. Small bowel films recorded after barium was given orally showed a long, narrowed segment which suggested a localized enteritis. The remaining films led the radiologist to suspect a tumor.

The preoperative diagnostic impression was intermittent small bowel obstruction due to one of the following: (1) benign small intestinal tumor or polyp; (2) malignant intestinal tumor; (3) Meckel's diverticulum; or (4) regional enteritis.

Malignancy was not strongly suspected since symptoms had been present for two years. The patient was considered to be above the usual age for Meckel's diverticulum.

On February 4, 1952, surgery was performed and an ileoileal intussusception was found and readily reduced. The bowel was thickened

FIG. 1. Case II. Shows the intussuscipiens receiving the intussusceptum at the time of the operation.

distally and proximally but was quite viable. A tumor was palpable within the lumen of the distal ileum where a small umbilication was noted on the antimesenteric border. This represented the point of attachment of Meckel's diverticulum. The appearance of the intussusception is shown in Figure 1.

Resection of the mass with a segment of ileum was performed and end-to-end anastomosis completed. The open ileum is photographed to show the lesion from within the intestinal lumen. (Fig. 2.)

Examination of the specimen proved that it was invaginated Meckel's diverticulum. This was the leading point of the intussusception. No gastric or pancreatic tissue was found in the diverticulum. The patient made an uneventful recovery and was discharged on the tenth postoperative day.

At this point it is well to present a brief review of cases of intussusception due to Meckel's diverticulum collected from the literature from 1933 to 1954.

Aitken.[8] An eight month old female infant had had attacks of pain for one month. The present illness of twenty-four hours was characterized by abdominal colic, vomiting, distention and the presence of rectal blood and mucus. A rectal mass was palpable. At surgery an intussusception was found and clear ab-

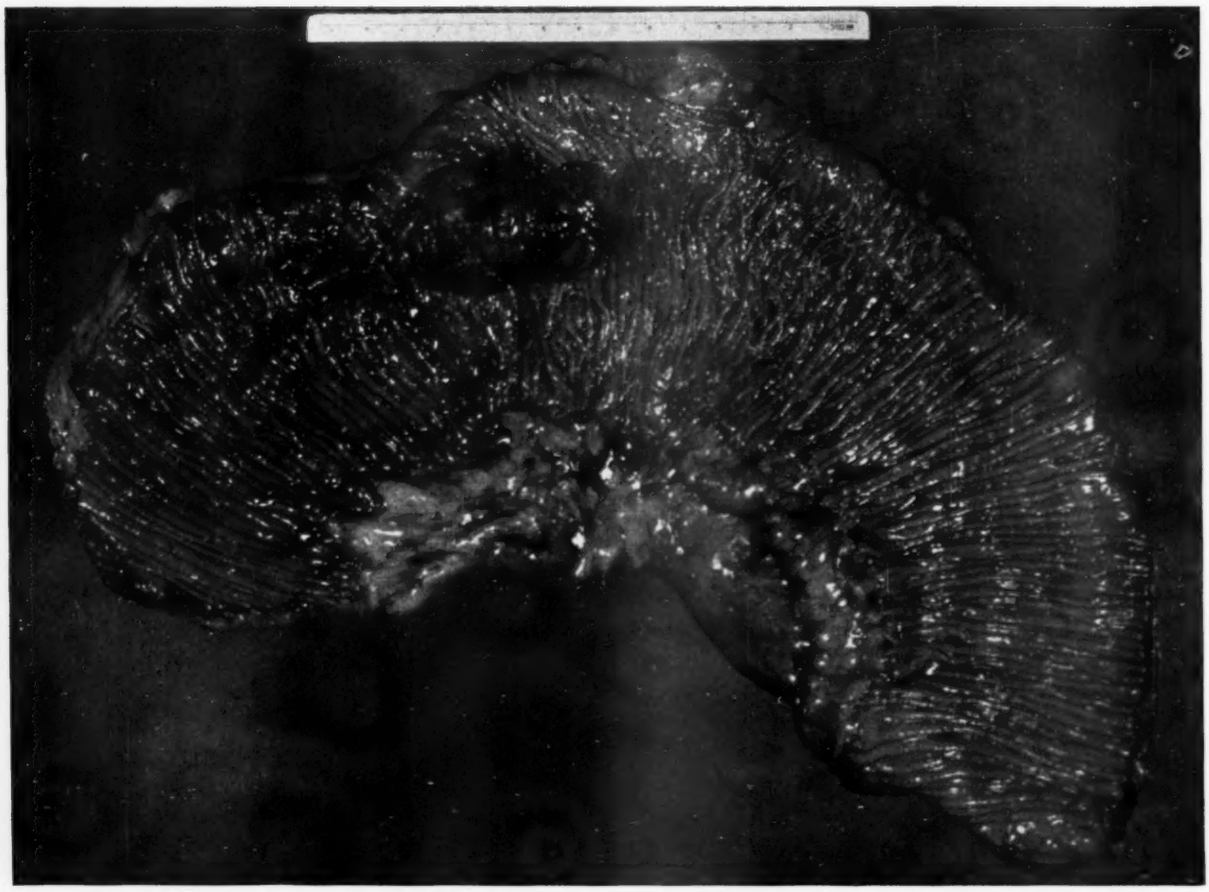

FIG. 2. Case 11. Shows the open specimen with the invaginated Meckel's diverticulum present in the lumen.

dominal fluid was present. Resection of the ileum and Meckel's diverticulum and side-to-side anastomosis were performed. The patient recovered but a postoperative hernia developed.

Atwood.[9] A seven year old boy had had no previous attack. The present illness of forty-eight hours was characterized by severe abdominal pain, vomiting, distention and abdominal tenderness. He was lethargic and cyanotic. An acetone odor of the breath was noted. The temperature was 100.6°F.; the pulse was 130. Neither a rectal mass nor blood was described. At surgery, foul-smelling fluid was encountered upon opening the peritoneal cavity. The patient was severely ill, and reduction was the only procedure performed. Severe electrolyte imbalance was present but no laboratory data were recorded. Severe dehydration and acidosis undoubtedly contributed to this patient's death one hour postoperatively.

Barcley.[10] This seven year old girl had had no previous attack. The present illness was characterized by colicky abdominal pain and vomiting. No mass was palpable on abdominal examination. A rectal mass was present but no blood was noted. Reduction of the intussusception and excision of Meckel's diverticulum were accomplished. Gastric mucosa was seen on microscopic examination. The patient recovered.

Blanco.[11] This thirty-three month old male infant had had a previous attack two months before admission. The present illness of less than twenty-four hours was characterized by severe abdominal pain and vomiting. A mass was palpable in the right lower quadrant of the abdomen. The rectal examination revealed blood. The patient appeared toxic and dehydrated. Acetone was present in the urine. At surgery turbid peritoneal fluid was present. Reduction of the intussusception and excision of Meckel's diverticulum were performed. No chemical laboratory data were available. Acidosis contributed to this patient's death five hours postoperatively.

Bowen.[12] This fourteen year old boy had no

record of any previous attacks. The present illness of three hours' duration was characterized by abdominal colic, vomiting, tenderness and rigidity in the right lower quadrant of the abdomen. An abdominal mass was palpated after rigidity was controlled with general anesthesia. No rectal mass or rectal blood were present. Reduction of the intussusception, excision of the diverticulum and appendectomy were performed. Microscopic examination revealed gastric mucosa. Traction was used on the ileum to reduce the intussusception. The patient recovered.

Caminiti.[13] This forty-seven year old man had a history of previous attacks three years, five months, two months and one month before admission. On admission, severe colicky abdominal pain was noted; vomiting, distention, tenderness and rigidity were also present. An abdominal mass was felt but no rectal mass or blood were noted. Resection and end-to-end anastomosis were performed and the patient recovered.

Campbell.[14] This nineteen year old man had had previous attacks of pain for twelve years. The present illness was characterized by cramping abdominal pain, vomiting and a palpable mass in the right lower quadrant of the abdomen. These signs and symptoms which were present on admission had also occurred ten days previously. Rectal blood was present but no mass was palpated. Resection and end-to-end anastomosis were performed. Gastric mucosa was seen on microscopic examination. This is an unusual case in that the patient had such a long history of abdominal pain (twelve years). He made a good recovery.

Carnazzo.[15] The patient was a seven year old boy. He had a recent history of severe abdominal pain and projectile vomiting. Enemas failed to give relief. Abdominal tenderness and rigidity were present and an abdominal mass was felt. Surgery revealed that 30 cm. of the ileum invaginated into the cecum. Reduction was performed and Meckel's diverticulum was excised; appendectomy was also performed.

Chabrillat.[16] This thirty-nine year old man had had several previous attacks. His present illness was characterized by abdominal colic. Vomiting was not described. Rectal blood was noted. At surgery resection and end-to-end anastomosis were performed. The patient recovered.

Clark.[17] The present illness of this twenty-two year old man was characterized by colicky, periumbilical abdominal pain, vomiting and tenderness. No abdominal or rectal mass was described. Surgery consisted of resection with side-to-side anastomosis. An associated volvulus was present. The patient recovered.

Clute.[18] This forty year old man had had an attack four weeks prior to admission. The present illness of one day's duration was characterized by cramp-like periumbilical pain, vomiting, distention and rectal blood. This patient, like the one in Case II, was thought to have a duodenal ulcer because of severe pain, shock and black stools. The presence of an ulcer would not explain the cramp-like pain, distention or the borborygmi. X-ray examination suggested regional enteritis or a new growth. The patient made an uneventful recovery after surgery.

Del Campo.[19] This twenty-seven month old male infant had a history of previous attacks. The present illness of two days' duration was characterized by colicky abdominal pain but apparently no vomiting. An abdominal mass was present in the right lower quadrant of the abdomen. At surgery cloudy peritoneal fluid was noted. Reduction of the intussusception with excision of Meckel's diverticulum was performed. Microscopic examination revealed pancreatic tissue. The patient recovered.

Duncan.[20] This nine year old boy had had no previous attacks. His present illness of five days' duration was characterized by colicky abdominal pain, vomiting and tenderness. An abdominal mass was palpable in the right lower quadrant of the abdomen. Exteriorization and resection were done; five days later anastomosis was performed. The patient recovered.

Foster.[21] This patient, a sixteen year old boy, had had no previous attacks. The present illness of twenty-six hours' duration was characterized by colicky abdominal pain, vomiting and a palpable mass in the right lower quadrant of the abdomen. No rectal blood or rectal mass was described. Reduction and excision of the diverticulum as well as appendectomy were performed. Microscopic examination revealed the presence of a submucous lipoma. The patient recovered.

Gadbois.[22] This patient, an eight year old boy, had had no previous attacks. The present illness of six days' duration was characterized by colicky abdominal pain, vomiting and tenderness to palpation. Abdominal examina-

tion revealed a mass in the right lower quadrant of the abdomen and rigidity. Resection was performed and the patient recovered.

Gay.[23] This patient, a twenty year old woman, had a three-day history of intermittent, cramping abdominal pain, nausea, vomiting and distention. X-ray studies showed gaseous distention of the small bowel. At surgery an ileoileal intussusception due to invaginated Meckel's diverticulum was seen. Resection and end-to-end anastomosis were done. The pathologic diagnosis was Meckel's diverticulum showing gastric mucosa and gangrene of the small intestine. The patient survived.

Gay.[23] This thirty-one year old man had a two-week history of anorexia and severe periumbilical pain but no vomiting. Before admission he had watery diarrhea and later melena as well as pain. He passed tarry stools. Physical examination revealed tenderness in the lower portion of the abdomen and a questionable mass in the right lower quadrant of the abdomen but no rectal mass. Stool examination was positive for occult blood. At surgery an ileoileal intussusception due to invaginated Meckel's diverticulum was seen. Resection and end-to-end anastomosis were performed. The pathologic report described Meckel's diverticulum. The patient recovered.

Gibbins.[24] This patient, a twenty-eight year old woman, had periumbilical pain when active. Symptoms were not related to food intake. The attacks lasted six months; the patient was then asymptomatic for two and a half years. Later she had several attacks of severe pain. There was no vomiting at any time. No abdominal or rectal mass was felt. X-ray studies were not helpful. At surgery an ileoileal intussusception was found 30 cm. from the ileocecal valve. Resection was performed. The pathologic specimen proved to be Meckel's diverticulum containing heterotrophic gastric duodenal, colonic and pancreatic tissue, and a lipoma. Peptic ulceration was present. The patient recovered.

Gilles.[25] This two and a half year old boy had had no previous attacks. The present illness was characterized by episodes of screaming with pain and a palpable mass in the right lower quadrant of the abdomen. No rectal mass was felt. Resection was performed with end-to-end anastomosis. An uneventful recovery followed.

Godard.[26] This twenty-five year old man had had no previous attacks. The present illness of seven days' duration was characterized by colicky abdominal pain, vomiting, distention and tenderness. No abdominal mass or rigidity was present. Rectal blood was noted but no mass was present. At surgery serous fluid was noted. Because of the poor condition of the patient, the intussusception was exteriorized. The patient died twenty-three hours after surgery.

Gray.[27] This patient, a thirty-seven year old woman, had a rather unusual history of vague epigastric pain for a period of six years with no nausea or vomiting. However, an abdominal mass was palpated. Rectal bleeding was not described. Resection with end-to-end anastomosis and enteroanastomosis was performed. Microscopic examination revealed adenocarcinoma, grade 2 arising in the ectopic gastric mucosa of Meckel's diverticulum. The patient survived.

Greenfield.[28] This patient, a twenty-three year old man had had no previous attacks. The present illness began two days before admission and was characterized by colicky abdominal pain, vomiting, abdominal tenderness and a palpable rectal mass. At surgery bloody peritoneal fluid was noted. Resection was performed with end-to-end anastomosis. Recovery was uneventful.

Grigorescu.[29] This patient, a forty-three year old woman, had a history of abdominal pain and nausea of ten months' duration. Four days before admission she again noted abdominal pain and vomited. On admission she was acutely and severely ill. The abdomen was soft with tenderness in the right lower quadrant where a mass was palpable. Rectal examination revealed no mass or blood. At surgery an irreducible ileoileal intussusception was noted together with non-viable bowel. Resection of the mass and side-to-side anastomosis were performed. Pathologic examination of the specimen revealed invaginated Meckel's diverticulum. The patient recovered.

Hallstrom.[30] This two month old male infant vomited slightly after meals for two weeks. Three hours before admission the vomiting was more severe and blood-tinged vomitus was seen. The child was pale and weary. The abdomen was distended and distended loops of bowel were seen. The abdomen was soft with a "resistance scarcely as large as a walnut" above the umbilicus. No rectal blood was observed.

X-rays suggested the presence of intussusception. Reduction of the intussusception with excision of the diverticulum was performed. The outcome was not described.

Hanelin.[31] This twenty-five year old man had had previous attacks for two years. The present illness of two weeks was characterized by colicky abdominal pain, vomiting, distention and abdominal tenderness. No rectal or abdominal masses were felt but rectal blood was noted. Resection with end-to-end anastomosis was performed. The patient recovered.

Harrenstein.[32] This seven year old girl became very ill after a sudden onset of pain and vomiting which recurred a number of times. Constipation was present but no blood or mucus was passed per rectum. An abdominal mass was present. Reduction of the intussusception and resection of invaginated Meckel's diverticulum were performed. Progress was poor and at a second operation enteroenterostomy was carried out with eventual recovery.

Harris.[33] This fourteen year old boy had had no previous symptoms. His present illness was characterized by generalized abdominal pain of two days' duration. Vomiting was present and there was abdominal tenderness but no rigidity. No rectal mass was palpated. Reduction of the intussusception and resection of the ileum with anastomosis were performed. The patient recovered.

Klingenstein.[34] This seven year old boy had recurrent symptoms for nineteen days. The present illness of twelve hours' duration was characterized by severe colicky periumbilical pain and vomiting. No rectal or abdominal mass could be felt and no rectal bleeding was noted. Two weeks previously he had been observed for five days because of a similar attack. Reduction of the intussusception with excision of the diverticulum and appendectomy comprised the surgical treatment. Gastric mucosa was present upon microscopic examination. Recovery was reported after surgery.

Korzun.[35] This seven month old male infant had had no previous symptoms. The patient cried with pain. Distention, tenderness and rigidity were present and rectal blood was noted on examination. Resection with side-to-side anastomosis was performed. This patient had a bloody exudate at surgery and I believe that peritonitis was present in view of the aforementioned findings. He died two hours postoperatively from "circulatory failure."

Kozalka.[36] This twenty-six year old man had intermittent cramping abdominal pain and vomiting recurring with each meal. The stool was streaked with red blood. A similar episode had occurred three years before admission. X-rays for peptic ulcer at that time gave a negative result. Physical examination was not unusual. No masses were noted on abdominal palpation or rectal examination. The stool was positive for occult blood. Symptoms were contollled by placing the patient on a Sippy diet for two months but the anemia was not corrected. At surgery intussusception due to invaginated Meckel's diverticulum was found. Resection was performed with end-to-end anastomosis. The pathologic specimen proved to be Meckel's diverticulum with gastric and pancreatic heterotrophic tissue as well as peptic ulceration. Recovery followed and the patient was discharged twelve days postoperatively.

LeFrancois.[37] This thirteen year old boy had no previously recurrent symptoms. The present illness was described as being acute and was characterized by colicky abdominal pain without vomiting, but tenderness was present. On examination an abdominal mass was palpable. There was no rectal mass or blood. Reduction of the intussusception and excision of the diverticulum were performed and recovery followed.

Leiter.[38] This patient, a fourteen year old boy, had had no previous symptoms. The present illness of three days' duration was characterized by colicky abdominal pain and vomiting. Physical examination revealed no distention tenderness or rigidity. An abdominal mass was present. No rectal mass or blood was noted. No abdominal exudate was noted at surgery and the intussusception was not reducible. Resection was performed with ileotransverse colostomy. Meckel's diverticulum contained ectopic gastric mucosa.

Levering.[39] This fifteen year old boy had had no previous symptoms. The present episode of eight days' duration was characterized by colicky abdominal pain and vomiting. Resection of part of the ileum together with Meckel's diverticulum and ileostomy were performed. The patient recovered.

Ley.[40] This five month old female infant had an acute illness of thirty-six hours' duration characterized by severe abdominal pain and vomiting. An abdominal mass was palpable under ether anesthesia. Reduction was per-

formed. Resection will be considered when the patient is three or four years old. The patient recovered.

Lozoya.[41] This five month old male infant had had no previous symptoms. The present illness of fifteen hours' duration was characterized by severe abdominal pain, vomiting and tenderness upon palpation. An abdominal mass and a rectal mass were demonstrated. Rectal blood was present. Laterolateral anastomosis was performed, and a portion of the ileum together with Meckel's diverticulum was excised. The recovery was uneventful.

Lozoya.[41] This five month old male infant had had no previous symptoms. The present illness of twenty-four hours' duration was characterized by abdominal pain and vomiting. An abdominal mass and rectal blood were noted, but there was no rectal mass. This is one of two patients who vomited blood. Resection of the diverticulum with a portion of the ileum was performed, as well as laterolateral anastomosis. The patient recovered following surgery.

Martin.[42] This fourteen year old boy had had no previous illness relating to the gastrointestinal tract. The present illness of two hours' duration was characterized by severe, colicky abdominal pain but no vomiting. Tenderness and abdominal rigidity as well as an abdominal mass were found upon palpation. No rectal blood or mass was described. Reduction of the intussusception and resection of the diverticulum were accomplished. Microscopic examination revealed gastric mucosa. The patient recovered.

McKechnie.[43] This forty year old man had had recurrent symptoms for five to eight weeks. The present illness was characterized by periumbilical cramping pain of two to three days' duration and vomiting. Examination revealed a mass in the left lower quadrant of the abdomen. Rectal examination revealed a palpable mass and rectal blood. Reduction of the intussusception with excision of Meckel's diverticulum was performed. Microscopic examination revealed ectopic gastric mucosa. The patient recovered following surgery.

Nedelec.[44] This fifty-two year old woman had had no previous symptoms. The present illness was described as being acute and characterized by severe, colicky abdominal pain and vomiting. On examination an abdominal mass was palpated. There was no rectal mass or blood. Right hemicolectomy with ileotransverse colostomy was performed. Laterolateral anastomosis was done. The patient recovered.

Padalino.[45] This six year old boy had had no previous symptoms. The present illness of twenty-four hours' duration was characterized by severe, intermittent, cramp-like pain which caused the child to draw up his legs. Vomiting, distention and tenderness were noted. There was a mass in the right lower quadrant of the abdomen. Reduction of the intussusception and excision of the diverticulum were performed. The patient recovered.

Paul.[46] This fifty year old man had had no previous symptoms referable to the intestinal tract. The present illness of two days' duration was characterized by colicky abdominal pain, distention and vomiting of blood. No rectal or abdominal mass was noted. Resection of the ileum and the diverticulum and end-to-end anastomosis were performed. The patient recovered following surgery.

Penberthy.[47] This nine month old male infant had no history of previous illness. The present episode began eight hours before admission and was characterized by severe cramp-like abdominal pain causing the infant to assume the knee-chest position. Vomiting and a mass in the right lower quadrant of the abdomen were present. The intussusception was reduced and the diverticulum was excised. The patient recovered following surgery.

Pool.[48] This thirty-five year old woman had had no previous symptoms. However, during previous pelvic surgery at another hospital, Meckel's diverticulum was an incidental finding and the ill advised procedure of inversion of the diverticulum was performed. The present illness was of three days' duration and was characterized by crampy abdominal pain, vomiting, distention and tenderness. There was no rectal mass. Reduction of the intussusception and resection of the ileum and diverticulum were performed. The patient recovered.

Reiser.[49] This patient was thirty-three years old. No reference was made to sex. The present illness was characterized by colicky abdominal pain, vomiting, distention and tenderness. Meckel's diverticulum and a portion of the ileum were resected and primary anastomosis was performed. Microscopic examination revealed ectopic pancreatic tissue. The final outcome was not described.

Rigattieri.[50] This twelve year old girl had abdominal pain of 7 days' duration with vomit-

ing and rectal bleeding. Abdominal examination revealed pain in the right lower quadrant of the abdomen and a movable mass. Surgery was performed and the intussusception was found to be due to invaginated Meckel's diverticulum. Resection and end-to-end anastomosis were performed. The patient recovered.

Salvo.[51] This fifty-one day old infant had had no previous symptoms. The present illness of one day's duration was characterized by severe pain, causing the patient to cry. A mass in the right lower quadrant of the abdomen and rectal blood were demonstrated. The patient was gravely ill. At surgery only reduction of the intussusception was performed. The infant died from "paleur hyperthermie."

Sprague.[52] This twenty year old man had had no previous symptoms. The present illness of one day's duration was characterized by abdominal cramps and vomiting. Reduction of the intussusception and excision of the diverticulum were performed. The patient recovered.

Stuppel.[53] This three year old girl had a history of recurring attacks of abdominal pain for three years. The present illness of twelve hours' duration was characterized by severe, colicky abdominal pain and vomiting. An abdominal mass was palpable but no mass was noted on rectal examination. At surgery, since the sheath was described as being healthy, lateral anastomosis was performed between the entering and sheathing layers 1 or 2 inches beyond the extremities of the loop and the mass was returned to the abdomen. The patient did not progress well and two days later the abdomen was re-entered. At this time patches of gangrene were noted on the sheath of the intussusception. Resection of the loop was performed leaving the anastomosis intact. The patient recovered following this unusual procedure.

Trempe.[54] This four year old boy had had no previous difficulty. The present illness began five days before admission with cramping abdominal pain, vomiting, distention, tenderness and rigidity. No note of a rectal mass was made. Resection of Meckel's diverticulum with a portion of the ileum was performed. Peritonitis was present. The reduced ileum was gangrenous, and therefore was resected. The patient died on the fifth postoperative day.

Wilson.[55] This nineteen year old girl had had no previous symptoms. The present illness began twenty-four hours before admission and was characterized by severe lower abdominal pain and vomiting. The intussusception was reduced and, Meckel's diverticulum was excised and appendectomy was performed. The outcome was not described.

Womack.[56] This eleven year old girl had had no previous symptoms. The present illness began six days before admission and was characterized by sharp, shooting periumbilical pain, vomiting, distention and tenderness. Rectal examination revealed blood. Surgery consisted of resection of the intussusception with formation of a double-barreled ileostomy. This was later closed and the patient recovered.

Ponka. Two cases by the author have been previously reported in this paper.

In addition to the aforementioned cases, Meckel's diverticulum associated with intussusception has been described by Casper,[57] Hugel[58] and Migliaccio.[59] However, because it is uncertain whether the diverticulum was inverted into the ileum these cases were excluded.

A consideration of the data gathered from this series reveals that the age of the patients varied from age fifty-one days to fifty-two years. Most of the patients were under thirty. In nineteen patients this condition occurred during the first nine years of life; three of these patients were less than one year old. Figure 3 illustrates the age distribution of this series as compared with that of Harkins.

The increased incidence in males is a common observation, and a ratio such as that from the series presented herein is frequently seen (thirty seven males to sixteen females). The sex of one patient was not given.

Chronic or recurrent symptoms were present in seventeen of fifty-four cases. One patient had recurring episodes of abdominal pain for twelve years. Other patients had symptoms for three and one-half years, three years, two years, one and one-half years or shorter periods. Chronic episodes occur more frequently in adults; this is an important factor to be remembered. One of our patients had recurrent episodes of cramping abdominal pain for two years. Thus, although these patients generally have acute intermittent abdominal pain, there is, not uncommonly, a history of previous attacks.

The duration of acute episodes varies considerably. Some patients were seen after symptoms had been present for two hours; others

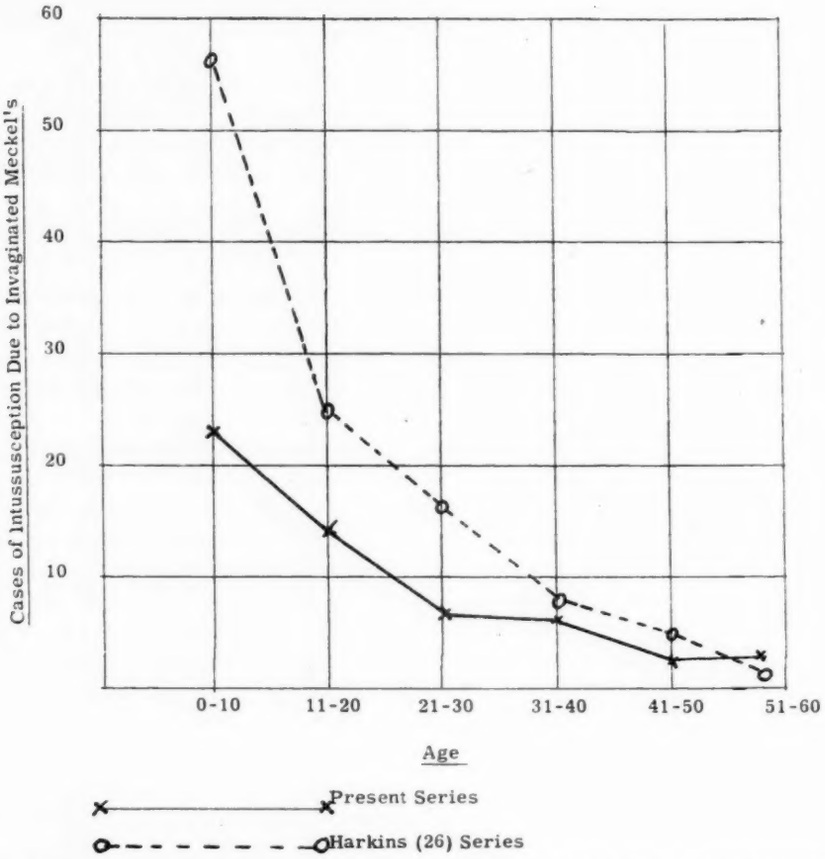

FIG. 3. Comparison of the age incidence of intussusception due to invaginated Meckel's diverticulum of this series with that of Harkins.

endured their illness for as long as two weeks. Thirty-four of the patients presented themselves for care within three days of the occurrence of symptoms and twenty-two were seen within twenty-four hours.

The pain was colicky and severe in forty-eight of the fifty-four patients. In infants this was manifested by screaming with pain and a drawing up of the legs. Most frequently the pain was periumbilical, although in two instances it was located in the lower portion of the abdomen. In one case it was described as being generalized; in only one patient was it described as being "vague."

Vomiting was noted in forty-six of fifty-four cases; four patients apparently did not experience this symptom. In the remainder of the cases vomiting was not mentioned. Blood was noted in the vomitus of two patients.

Meteorism or distention was present in nineteen cases. Tenderness was noted in twenty-seven cases. Rigidity was present in only seven cases. The presence of tenderness, rigidity and meteorism suggest peritonitis and the prognosis is grave. An abdominal mass was present in thirty-one cases.

A rectal mass was present in eight cases. Rectal blood was demonstrated in either the stool or upon rectal examination in eighteen cases.

An interesting observation was that the triad of findings including (1) abdominal mass, (2) rectal mass and (3) rectal blood occurred in some combination in forty-one of fifty-four patients (77 per cent).

The surgical procedures performed and their results are listed in Table II. In two cases the outcome was not described.

In suture technic, end-to-end anastomosis was used in fifteen cases; side-to-side anastomosis was performed in nine cases and the procedure used in the remaining cases was not well described.

An accompanying appendectomy was performed in five instances without a fatality.

The surgical procedure indicated in any

given case depends upon the findings. It must be remembered that simple reduction fails to deal with the lesion responsible for the intussusception, if a lesion is demonstrable.

Reduction of the intussusception and excision of the diverticulum is effective treatment when the ileum is viable. If there is doubt as to the viability of the ileum containing the diverticulum, resection should be performed.

TABLE II
SURGICAL PROCEDURES AND RESULTS

Procedure	Cases	Deaths
Reduction of intussusception only	3	2
Reduction and excision of diverticulum	17	1
Resection of ileum with diverticulum	31	3
Exteriorization	3	1

In critically ill patients exteriorization should be considered. We believe that with careful attention to the hydration of these patients they will do well, even with a functioning ileostomy, for short periods. We do not advise routine appendectomy in these cases.

The results (Table III) are interesting since the mortality rate has been reduced to approximately 20 per cent even when the two cases in which the results are not available are included in the deceased group. This is a remarkable improvement inasmuch as the mortality statistics referred to by Harkins[1] ranged from 35 to 74 per cent in selected groups of cases. In other words, in the last twenty years the mortality rate has been reduced at least 15 per cent in cases of intussusception due to invaginated Meckel's diverticulum.

From such a review interesting information can be gathered. In the case described by Pool,[48] Meckel's diverticulum was found during previous pelvic surgery and the ill advised procedure of inverting the diverticulum was performed before Dr. Pool saw the patient. Intussusception later developed and at a subsequent admission Dr. Pool resected the lesion successfully.

The clinical picture should be one familiar to everyone, and early surgery advised. Prolonged vomiting and inadequate fluid intake with consequent dehydration and acidosis was responsible for at least three of the seven deaths.

During this study I was impressed with the deficiency of laboratory data, including determinations of the chlorides, carbon dioxide combining power, non-protein nitrogen, and sodium and potassium levels. It is realized that sodium and potassium determinations were not readily available until recently. Proper hydration is absolutely necessary before surgery is undertaken.

TABLE III
RESULTS

	No. of Patients
Recovered	45
Died	7
Not stated	2

I believe that after hydration and blood replacement fairly extensive procedures can be performed with probable success. Antibiotics, postoperative intravenous fluids and decompression of the gastrointestinal tract are essential in the postoperative care of the patient.

One writer described reduction of an intussusception by applying traction on the ileum. I prefer the "milking procedure" applied at the caudal end of the mass.

Eleven of the cases presented had interesting findings upon microscopic examination of the specimen: gastric mucosa, ten cases; pancreatic tissue, three cases; lipoma, submucous, one case and adenocarcinoma, grade 2, one case.

SUMMARY AND CONCLUSIONS

1. Fifty-four cases of intussusception due to invaginated Meckel's diverticulum are reviewed.

2. Important symptoms include a sudden onset of severe, cramping, periumbilical pain with vomiting, decreasing bowel movements and passage of blood and mucus.

3. Forty-one of fifty-four patients (77 per cent) presented either one or a combination of this triad of findings: an abdominal mass, a rectal mass or rectal blood.

4. Early surgery should be urged but it presupposes early diagnosis which is of the greatest importance.

5. More attention to the state of fluid and electrolyte balance preoperatively will help to improve the results. Surgery in critically ill patients should be withheld until proper hydration is achieved and the chemical balance is at least partially attained.

6. The mortality rates are improving and during the past twenty years fifty-four patients were treated, with a mortality rate of approxi-

mately 20 per cent. Seven patients died. The outcome in two cases was not described. This represents a decrease of at least 15 per cent in the death rate for this condition since 1933.

7. Adults with intussusception frequently give a long history of recurring bouts of periumbilical pain; in infants this does not hold true.

8. Surgery is the treatment of choice and warning is given against the use of enemas to achieve reduction, since reduction of the invaginated Meckel's diverticulum cannot be accomplished by this means. A competent ileocecal valve would further complicate the problem by preventing the medium used in the reduction from reaching the terminal ileum.

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Acute Appendicitis in Infancy and Childhood

A CRITICAL REVIEW OF SEVEN YEARS' EXPERIENCE IN A CHILDREN'S HOSPITAL

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IN the fifteen-year period from 1940 to 1955 the transactions of one of America's senior surgical associations record only four papers on the subject of acute appendicitis, two of these limited to the problem in infancy.

TABLE I
ABDOMINAL LESIONS IN INFANCY AND CHILDHOOD REQUIRING URGENT SURGICAL INTERVENTION
(Series of 586 cases in 24,000 admissions)

Condition	No. of Cases	Per cent
Acute appendicitis	300	51
Intussusception	42	7
Intestinal atresia and stenosis	27	4.6
Traumatic abdominal lesions	18	3
Meckel's diverticula	17	2.9
Incarcerated inguinal hernia	16	2.7
All other abdominal lesions	166	28.8

It has been said that it is time to cease writing and talking about a subject when that subject is thoroughly understood by all and there is unanimity of thought as to its management. A third condition might be added, i.e., when the accepted therapy has reduced the mortality rate to a negligible figure.

Appreciating these factors, it was considered worth while to analyze our experience at the Childrens Memorial Hospital in Omaha, which was officially opened in April, 1948. In the seven-year period to July, 1955, this institution has had 24,000 admissions. This review covers a consecutive series of 300 infants and children coming to surgery with a diagnosis of acute appendicitis. There were no mortalities during this period. Since a majority of our surgeons today spent years of their active practice in the presulfa, preantibiotic days, it is gratifying to note the changing picture which has occurred in the prognosis of this common surgical condition.

In infants and children acute appendicitis remains much the most common urgent abdominal condition requiring surgical intervention. (Table I.) In a compilation of 586 consecutive laparotomies performed in infants and children, acute appendicits was the surgical diagnosis in 51 per cent, followed by intussusception (forty-two cases), 7 per cent; intestinal atresia and stenosis (twenty-seven cases), 4.6 per cent; traumatic abdominal lesions (eighteen cases), 3 per cent; Meckel's diverticulum (seventeen cases), 2.9 per cent; and strangulated and incarcerated hernias (sixteen cases), 2.7 per cent.

TABLE II
AGE INCIDENCE IN 300 CLINICAL CASES OF ACUTE APPENDICITIS IN INFANCY AND CHILDHOOD

Age (yr.)	No. of Cases	Per cent
0–2	6	2
2–4	26	8.6
4–6	48	16
6–8	58	19
8–10	81	27
10–12	50	16.6
12–14	24	8
14–16	7	2.3

It is well appreciated that acute appendicitis is rare in children under the age of one year and quite infrequent in children before the second year. Thereafter through the years of childhood the disease rapidly increases in frequency.

(Table II.) In our own series only six patients were seen under the age of two, the highest incidence in the group being noted between the eighth and tenth years.

An analysis of symptoms is difficult to evaluate when many of the patients present themselves for examination before the sixth year. (Table III.) It is noteworthy, however, that when a history was obtainable, it followed the classical accepted sequence of Cope in 74 per cent of the entire series. If one considers only those patients found to have diffuse suppurative appendicitis, perforations or abscesses, the classical symptom complex was elicited in 90 per cent of the patients. Pain alone was the presenting complaint in 26 per cent of our group while urinary symptoms were noted in only 4.3 per cent. Fever was noted on examination in 94 per cent, ranging from 100° to 101°F. In two-thirds of the patients with perforated appendixes the temperature was above 101°F. on admission.

TABLE III
ANALYSIS OF SYMPTOMS IN 300 CLINICAL CASES OF ACUTE APPENDICITIS IN INFANCY AND CHILDHOOD

Symptoms	Per cent
Classical sequence	74
Anorexia	28
Pain only	26
Nausea but no vomiting	9.6
Diarrhea	9
Constipation	8.3
Urinary complaints	4.3
Previous laxative	11.6

The only reliable physical finding we have come to depend upon is localized tenderness with or without muscle-guarding or rigidity. This finding in the infant and child is quite as reliable as in older patients and was the one physical finding consistently present in this series. When combined with rectal examination, which may be very helpful in this group of young patients, the necessary information may usually be obtained on examination.

In the past much interest has been manifested in the seasonal variance of acute appendicitis. All accept an increased incidence during the early months of the year when respiratory infections are most frequent, with a second peak period in the very warm weather of midsummer. (Fig. 1.) A study of monthly variance in this series of 300 cases confirms this accepted idea, March being the month of highest incidence, followed by July and January, respectively.

Pathologically, we have divided this series of cases into four general types depending upon the findings at operation and the laboratory diagnosis. (Table IV.) In this correlation of age and pathologic findings, a high incidence of perforation with or without abscess is noted in the younger group, which is a common experience. This relationship may be more graphically demonstrated if similar material be shown in a block graph. (Fig. 2.)

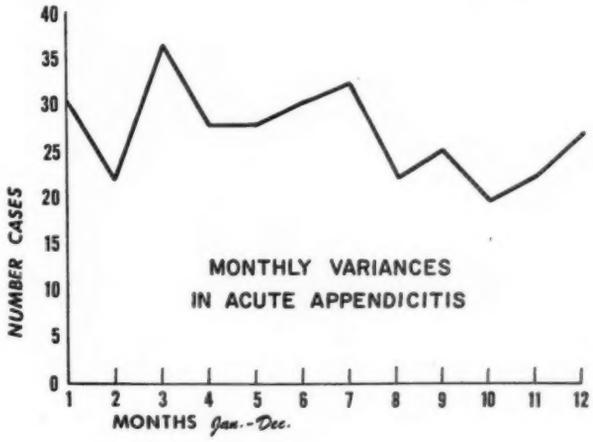

FIG. 1.

TABLE IV
CORRELATION OF AGE TO PATHOLOGIC DIAGNOSIS IN 300 CLINICAL CASES OF ACUTE APPENDICITIS IN INFANCY AND CHILDHOOD

Age (yr.)	Per cent of Cases in Total Series	Acute Focal	Acute Diffuse Suppurative	Perforated	Abscessed
0–2	2	1	2	2	1
2–4	8.6	11	3	9	3
4–6	16	26	17	4	1
6–8	19	33	20	4	1
8–10	27	42	31	7	1
10–12	16.6	26	14	8	2
12–14	8	14	7	2	1
14–16	2.3	5	2	0	0

A correlation of the length of the history, the hospital stay and the leukocytosis on admission found in the various types of appendicitis was of interest. (Table V.) A more detailed analysis of the leukocyte counts indicates that in such a group of young patients the leukocytosis varies tremendously but in general is very helpful.

The groups classified as having acute focal appendicitis and acute diffuse suppurative appendicitis were further studied in greater degree as to the leukocytic response. (Table VI.) One can only conclude that in infants and children, as in adults, the white blood count is

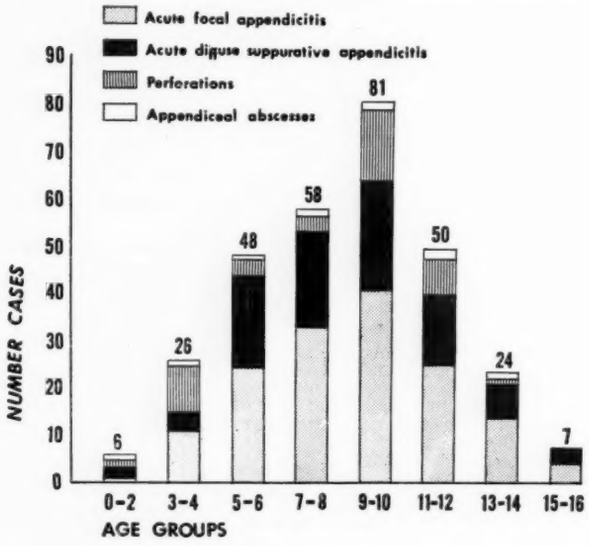

FIG. 2.

helpful if it fits in with the history and the clinical picture. However, it should not be considered as important as the physical findings in a decision as to choice of procedure.

This group of patients was operated upon by the attending surgical staff of the Childrens Memorial Hospital, so that there was some difference in the technical management of the series. A McBurney incision was employed in 60 per cent, a transverse incision in 17 per cent, a right rectus incision in 15 per cent and a Davis or paramedian incision in 8 per cent. The appendiceal stump was simply ligated in 87 per cent and inverted following ligation in 13 per cent. Of those cases which were perforated but without definite abscess, 58 per cent were closed with drains into the peritoneal cavity. The remaining cases in the perforated group without abscess were closed tightly without serious complication.

The ten patients with appendiceal abscesses merit additional comment. They had been ill an average of six and a half days on admission and some were extremely toxic when first seen on the surgical service. After suitable preparation with fluids, blood if indicated and antibiotics, eight of these ten patients underwent surgery. In three patients, only drainage of the appendiceal abscess was accomplished, with subsequent appendectomy three months later. In five of the eight cases primary appendectomy was carried out with drainage of the abscess. Two cases were handled conservatively with resolution of the abscess and the recommenda-

TABLE V

300 CLINICAL CASES OF ACUTE APPENDICITIS IN INFANCY AND CHILDHOOD

	Acute Focal (158 Cases), 52%)	Acute Diffuse Suppurative (96 Cases, 32%)	Perforations (36 Cases, 12%)	Appendiceal Abscesses (10 Cases, 3.2%)
Length of history (average no. of days)	1.7	2.2	3	6.5
Hospital stay (average no. of days)	3.8	4.4	9.1	12.7
Leukocytosis (average)	11,000	19,800	23,000	27,000

TABLE VI

EVALUATION OF WHITE BLOOD COUNTS IN 300 CLINICAL CASES OF ACUTE APPENDICITIS IN INFANCY AND CHILDHOOD

Type of Appendicitis	Highest Count	Lowest Count	Mean Average
Acute diffuse suppurative appendicitis (96 cases)*	65,000	5,400	19,800
Acute focal appendicitis (158 cases)†	32,300	4,500	11,000

* Count between 13,000 and 23,000, 65 cases (68%); count below 9,000, 9 cases (9.3%); count above 30,000, 12 cases (12.5%).

† Count below 7,000, 13 cases (18.2%); count above 20,000, 8 cases (5%); count between 7,000 and 12,000, 106 cases (65%).

tion that subsequent appendectomy be performed. It is noteworthy that these two patients have not returned for appendectomy. This fact definitely represents one of the hazards of this method of treatment if the patient does not have an understanding and cooperative family.

In this series of cases of acute appendicitis, including those with perforation and abscess, there has been no mortality. This result is ascribed to earlier diagnosis, prompt surgery when indicated, better anesthesia, and a general understanding of fluid balance and antibiotic therapy.

SUMMARY AND CONCLUSIONS

1. A consecutive series of 300 cases of acute appendicitis seen in a new children's hospital is reported.

2. Twelve per cent of the patients in this series were admitted with perforated appendixes, and 3.2 per cent with appendiceal abscesses.

3. There was no mortality in this consecutive series, which was handled by a group of surgeons with somewhat different technical methods.

4. Acute appendicitis in infancy and childhood, while still potentially a very serious disease, is rapidly becoming one of those which is well understood by the profession. Therapy is becoming standardized and results are approaching the ideal.

When a cervical rib is present and the patient has symptoms indicative of pressure on the neurovascular bundle at the cervicobrachial junction, excision of this rib plus severance of the tendon of the scalenus anticus is definitely indicated if physiotherapy does not suffice. If no cervical rib is present and conservative therapy is unsatisfactory, surgery is again advisable. However, not only must the scalenus anticus be cut but also thorough exploration of the brachial plexus may indicate that some other structure might be contributing to the causation of this syndrome. If so, it also must be removed if possible. (*Richard A. Leonardo, M.D.*)

Obturator Hernia

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OBTURATOR hernia has been recognized as a surgical condition since de Ronsil reported the first case to the Royal Academy of Science in 1724. In 1743, Garengeot reported seven other cases, and in 1726, Camper described the anatomy of this type of hernia. G. de Ronsil, son of Arnoud de Ronsil, reported the first case in which a strangulated obturator hernia was reduced successfully by taxis. Several others reported they had performed laparotomy for cases of strangulated hernias, but their patients died. According to Hilton, the first case successfully detected and operated upon with recovery was treated by Henry Obre in 1850.

Rowe and Bynum, in 1950, reported a total of 455 cases of obturator hernia in the literature. Since that time only six cases have appeared in the literature. The two cases reported herein brings the total to 463 to July 1, 1955.

An obturator hernia is the herniation of intra-abdominal structures through the obturator foramen. The obturator foramen is described by Gray as a large aperture, situated between the ischium and pubis. In the male it is large and of oval form; in the female it is smaller and more triangular. It is bounded by a thin, uneven margin to which a strong membrane is attached, and presents superiorly a deep groove (the obturator groove). This groove is converted into a canal by a ligamentous band, a specialized part of the obturator membrane. The obturator canal is seldom more than 1 cm. in diameter and is constantly occluded by a distinct collection of pre-peritoneal fat. It is the occasional deficiency of the lipomatous barricade which allows a peritoneal process to dip into the canal. Through the canal the obturator vessels and nerve pass out of the pelvis.

The relationship of the neck of the sac to the position of the obturator vessels and nerve is somewhat variable. For practical purposes, there are three varieties: (1) the sac emerges from the external orifice of the obturator canal and follows the anterior branch of the vessels to lie in the upper part of thigh under the pectineus muscle; (2) the sac follows the inferior branches of the vessels and lies between the fasciculi of the obturator muscles; and (3) the sac enters the canal and develops between the two obturator membranes and comes to lie behind the obturator externus muscle. In most cases, however, the obturator artery is behind and lateral to the neck of the sac. The nerve is usually lateral to the sac and above the artery.

CASE REPORTS

CASE 1. A sixty-three year old white woman was admitted to the hospital on April 28, 1955, with the chief complaint of nausea and vomiting with cramping abdominal pain. The onset of symptoms had been on April 24, 1955. She stated on admission that most of the pain had been in the lower abdomen, particularly in the suprapubic area and in the lower left quadrant. The patient had had anorexia for about four years prior to this admission and had lost approximately 30 to 35 pounds during that time. She had normal bowel movements prior to the onset of the present symptoms. There was no history of tarry or bloody stools.

The past history revealed that the patient had had many admissions for chronic bronchiectasis. She had undergone several major operations: in 1926, subtotal hysterectomy and appendectomy; in 1936, laparotomy with cholecystectomy; in 1951, thoracotomy with left lower lobectomy; in 1953, cystocele repair; and in 1954, breast cyst removed.

The patient was a gravida III, para II (one miscarriage). She had had a cardiac condition for several years and at present was receiving digitalis. Systemic review revealed that the patient had a chronic cough with production of

copious amounts of foul-smelling sputum. Some degree of exertional dyspnea and occasional pedal edema was also present.

Physical examination revealed an acutely ill, extremely emaciated, white woman, appearing older than sixty-three years of age. Blood pressure was 96/50, pulse 92, temperature 98.6°F. and respirations 24. The abdomen was soft and flat; the liver, spleen and kidneys were not palpable. There was a feeling of resistance in the left lower quadrant but no definite mass could be palpated. Normal bowel sounds were present over the entire abdomen. Rectal and pelvic examination revealed a soft mass in the left pelvis which had the feeling of intestine. The patient complained of extreme tenderness in the left pelvis.

Minimal pedal edema was present in the extremities. The thighs revealed no tenderness or masses.

Laboratory findings on admission were as follows: red blood count, 4,480,000; hemaglobin, 13.5 gm.; white blood count, 29,250; differential: polymorphonuclears, 88 per cent; lymphocytes, 11 per cent; monocytes, 1 per cent; sodium, 129 mEq.; potassium, 4.77 mEq.; non-protein nitrogen, 57; carbon dioxide, 52.3 volumes per cent. Urinalysis revealed occasional hyaline casts and rare blood cells; the feces gave a negative result for occult blood.

The admitting diagnosis was: (1) possible carcinoma of the colon with partial intestinal obstruction; (2) arteriosclerotic heart disease with mild congestive failure; (3) chronic bronchiectasis.

The patient was followed up for several days. She was given fluids by venoclysis and had a gastrointestinal series which revealed a small bowel obstruction, most likely jejunum with the point of obstruction in the lower abdomen or pelvis.

The patient did fairly well following admission. No further vomiting occurred until May 4, 1955, when she became moderately distended and complained of cramping abdominal pain. She was taken to surgery on May 5th and under general anesthesia a left lower paramedian incision was made. Upon opening the abdominal cavity, no free fluid was encountered and the jejunum presented loops of distended and collapsed bowel. Examination of the collapsed portion of the small bowel revealed that the obstruction was a Richter type left obturator hernia. There was no evidence of impaired blood supply to the obstructed segment of small bowel. The jejunum was the involved segment and was freed by dissection, at which time gas promptly entered the distal segment. The sac, which was approximately 1 cm. in depth, was left in place and the peritoneum was brought up from below the obturator foramen and sutured to the superior edge of the foramen. The hernial sac was obliterated by incorporating the most distal segment of the sac in the interrupted sutures.

Additional history obtained one week postoperatively revealed that for the past four years the patient had had increasingly severe, intermittent, cramping pain in the left lower quadrant when the left thigh was flexed on the abdomen. Extending the thigh or lying down would give relief of the pain. The patient also stated at this time that she had had increasing anorexia for two years prior to this admission.

The patient had an uneventful convalescence and was dismissed ambulatory on the sixteenth postoperative day.

Case II. A fifty-nine year old white woman was admitted to the hospital on May 28, 1948, with the chief complaint of not feeling well the evening prior to admission. A few hours later a sharp abdominal pain developed associated with some vomiting of a clear liquid. The doctor was called to the house and advised hospitalization.

Past history revealed that the patient had been operated on for a ruptured gallbladder with removal of stones twenty years previously. The gallbladder was not removed at that time because of the patient's poor condition. Approximately fifteen years later "nervousness" developed and was subsequently diagnosed as "choreiform athetosis," probably due to generalized cerebral degeneration. Two years prior to admission the patient had had fusion of the right knee for arthritis.

Physical examination revealed the following data: blood pressure, 168/88; pulse, 80; temperature, 99.0°F.; and respirations, 22. A systolic murmur was present over the mitral area of the heart. A well healed high right rectus scar was noted on the abdomen. Generalized abdominal tenderness was present but no masses were palpable. There was no definite rigidity, but some tenderness was noted in the right flank. The abdomen was tympanitic. No tenderness was present over the right

femoral or inguinal areas. The admitting diagnosis was intestional obstruction.

Laboratory findings were as follows: urinalysis: albumin, trace; occasional white blood cells, occasional red blood cells; white blood cell count, 11,000; hemoglobin, 10.5 gm.; nonprotein nitrogen, 45.5; chlorides, 550.

A Miller-Abbott tube was inserted and the patient was followed up conservatively for two days. Flat x-ray of the abdomen on May 30, 1948, revealed gaseous distention of the stomach and small bowel down to the lower midabdomen. The large bowel was not distended. The impression was small bowel obstruction, probably the lower ileum.

The patient was taken to surgery on May 30, 1948, and under general anesthesia a right perirectus incision was made. Upon opening the abdominal cavity, a large amount of serous fluid exuded. A loop of the ileum was found caught in the right obturator foramen. After unsuccessful attempts to free the incarcerated bowel, the inferior medial portion of the obturator foramen was clipped to free the bowel. The bowel was found to be gangrenous; therefore, approximately 5 inches of the ileum was resected and side-to-side anastomosis was performed. The patient did well postperatively and was dismissed ambulatory on the eighteenth postoperative day. She had not had any recurrence of symptoms to date as far as we know.

COMMENTS

Obturator hernia occurs five to six times more frequently in women than in men. Frequent pregnancies cause a relaxation of the pelvic peritoneum and also tend to cause a thinning of the protective preperitoneal fatty layer or pad. Emaciation may remove this protective fatty layer. By far the majority of these hernias occur in persons sixty to seventy years of age; it is rarely seen in persons under fifty years of age. Chronic pulmonary diseases and chronic constipation are predisposing factors due to increased intra-abdominal pressure which these conditions produce.

Eventual strangulation is almost always the rule in obturator hernia. The unyielding nature of the internal opening of the canal, bounded above by the bony wall and below by the sharp edge of a firm, inelastic membrane, accounts for the apparent site and cause of the strangulation.

Obturator hernias descend through the obturator foramen into the obturator canal, which passes downward, medialward and forward in the upper aspect of the thigh. The hernia usually comes to lie just anterior to the external obturator muscle and immediately behind the pectineus and adductor longus muscles. Being tightly enclosed in muscle and fasia deep in the thigh, this type of hernia frequently does not produce a noticeable or palpable mass, which often calls attention to the presence of a hernia elsewhere in the body. This anatomic reason alone makes the diagnosis of the obturator hernia difficult. When the hernia is present in the canal it encroaches on the already limited space occupied by the structures present in the canal and produces pain or paresthesia over the distribution of the branches of the obturator nerve. This symptom was first described by Howship in 1840 and by Romberg in 1845 and is known today as the Howship-Romberg sign. Symptoms referable to this nerve distribution area are probably the most valuable aid in making the diagnosis of obturator hernia. Watson stated that this sign is present in over 50 per cent of cases.

Since the most common content of the sac of an obturator hernia is small bowel, the presenting complaint is frequently intestinal obstruction. Usually the sac is small, admitting only a portion of the diameter of the bowel, with a resultant Richter type hernia. Such was true of Case 1 reported herein. There have been instances of the sac containing bladder and fallopian tube, Meckel's diverticulum, infected fallopian tube with abscess formation, omentum and rarely cecum and appendix.

To aid in the diagnosis a careful search should be made in the upper inner part of the thigh for a palpable mass or localized tenderness. This symptom can be expected in a fairly high percentage of cases.

It will be recalled that the adductor longus, obturator externus and pectineus muscles act essentially as adductors, flexors and external rotators of the thigh. In visualizing the strangulation of a hernial mass caught between the obturator externus posteriorly and the adductor longus and pectineus anteriorly, one can readily understand that these patients will have more pain due to increasing pressure on the sac when the leg is extended, adducted and internally rotated. Finally, the demonstration of a tender mass on the anterior pelvic wall by

vaginal or rectal examination may help to verify the diagnosis.

TREATMENT

The treatment of an obturator hernia is surgical. An approach through the thigh has been advocated by some authors in the past but this method seems unwise, especially since the diagnosis is frequently uncertain and because of the limited exposure afforded by such a route. In order to manage any condition found, an adequate paramedian or rectus incision in the lower part of the abdomen, corresponding to the side of the localization of symptoms, is recommended. Placing the patient in the Trendelenburg position may be of considerable help in reducing the hernia. The condition of the sac contents and the size of the sac at the time of surgery will largely govern how the condition will be handled.

Many methods dealing with the sac have been reported. A simple purse string suture will be adequate if the sac is small. Suturing the sac to the parietal peritoneum after pulling the apex through the opening has been suggested by Horine. Wakely advocates ligating the sac and suturing a strip of the innermost fibers of the pectineus muscle at the periosteum of the obturator canal. Short reported the use of a piece of cartilage from the rib to fill the defect. Throckmorton used an implant of tantalum gauze to repair the defect. Rothman reported a repair using a peritoneal graft. Also, Stone and McLanahan utilized an osteoperiostal flap turned backward from the inner aspect of the pubic bone and fastened by sutures over the obturator opening. Our method of repair in the first case reported herein was to peritonealize the defect from below upward and incorporate the sac into the suture line which was located anterior to the foramen, thus repairing the defect and strengthening the parts surrounding the obturator canal. The general condition of the patient, the size of the hernia and the extent of resection, if necessary, must be taken into consideration. Good surgical judgment must be exercised in selecting the procedure with which to repair the defect in each instance.

SUMMARY

Two case reports of successfully operated obturator hernias are presented bringing the total number of cases reported in the literature to 463. The anatomy of the obturator area is described. The diagnosis is suggested by the history or presence of pain, the Howship-Romberg sign and the demonstration of a mass or tenderness on the anterior wall of the pelvis which can be felt by bimanual examination. The treatment is surgical through an adequate abdominal incision, and the type of repair depends upon the condition of the patient, the size of the hernia and the condition of the contents of the sac.

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Skin Necrosis Following Intravenous Use of Norepinephrine

REPORT OF SIX CASES

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NOREPINEPHRINE is being used widely in the treatment of shock and peripheral circulatory collapse due to medical and surgical conditions. It is usually administered intravenously in a concentration of 4 μg. per cc. of 5 per cent glucose solution or 0.85 per cent sodium chloride solution (one ampule containing 4 mg. of nor-epinephrine in 1,000 cc. of either solution) at a rate sufficient to maintain a systolic blood pressure of 100. Initially a rate of infusion of 40 to 50 drops per minute is recommended. The effect upon the blood pressure is almost immediate. After the first few minutes the rate of flow is reduced to 20 to 30 drops per minute.

No attempt will be made herein to evaluate the use of the drug. We would like to call attention again to one of the serious complications of its use, discuss the cause of this complication and suggest a method which might possibly prevent it.

The intense local vasospasm and necrosis of the skin at the site of the infusion has been reported previously.[1–8] In an extremity receiving an infusion of norepinephrine there is frequently a noticeable blanching of the skin at the point of injection and occasionally along the vein into which the injection is made. Occasionally the area about the vein becomes red and hard, as in phlebitis. Usually this subsides shortly after the infusion is discontinued but may remain for as long as twenty-four to forty-eight hours. In a small percentage of cases with marked involvement the blanched area becomes cyanotic and anesthetic. The bluish purple color does not disappear on pressure and within forty-eight to seventy-two hours the skin develops small and large vesicles containing a clear yellow fluid. This is followed by definite gangrene of the skin and subcutaneous tissue with irregular but sharply demarcated borders. The surrounding skin may be hyperemic.

In one report[5] ulceration and gangrene of the skin occurred in two of fifty-five cases; in another report[6] local vasospasm, cold skin and cyanosis developed in fourteen of thirty cases so treated. Superficial ulcerations were noted in several of these latter cases. We have no statistics of the frequency of this complication. At the Michael Reese Hospital, where norepinephrine is used frequently in treating shock associated with myocardial infarction[8] and surgical emergencies, we have observed six cases of gangrene of the skin following its use. The number of instances of severe local ischemia and transient phlebitis not associated with skin necrosis is not known but is undoubtedly much greater.

CASE REPORTS

CASE 1. A. A., a forty year old Negro man, was hospitalized on January 2, 1954, because of severe pain in the left flank and left chest associated with diarrhea and vomiting. Physical and roentgenologic findings suggested a diagnosis of left lower lobe pneumonia. The following day more severe chest pain developed and the patient went into shock. Norepinephrine (4 mg. in 1,000 cc. of 5 per cent glucose solution) was administered by venipuncture in the left upper extremity to maintain the blood pressure level. Thoracentesis revealed the left chest to be filled with fluid which grossly resembled vomitus. At thoracotomy a spontaneous perforation of the lower esophagus was

FIG. 1. Case IV. Extensive discoloration and bleb formation along the course of the left saphenous vein three days after intravenous injection of norepinephrine.

FIG. 2. Same case. Demarcation of the area of skin necrosis two weeks later. This was subsequently excised and a split-thickness skin graft applied.

discovered and repaired. Norepinephrine was administered for eighteen hours. About twenty-four hours after it was discontinued a large irregular reddish blue area with vesicles was noticed on the medial aspect of the left forearm and arm. The skin and subcutaneous tissue sloughed but the denuded area was epithelized from the periphery in about six weeks. The patient was discharged from the hospital on February 13, 1954.

CASE II. M. K., a sixty-one year old white man, was admitted to the hospital on January 20, 1955, because of pain in the joints and black discolored areas on the fingers and toes. A diagnosis of periarteritis nodosa was made after muscle biopsy, and cortisone therapy was instituted. Two weeks later, after incision of a sterile abscess in a buttock due to parenteral medication, severe diarrhea and shock developed. Norepinephrine was used as part of the management and was administered intravenously in the forearm. Paravenous infiltration on two occasions in this area caused no permanent local tissue changes. However, a cannula was inserted into the right saphenous vein at the ankle for further administration of norepinephrine and in spite of the absence of evident local infiltration of the solution, an area of skin proximal to the cannula, measuring 10 cm. by 4 cm., became cold and cyanotic and vesicles developed within twenty-four hours. The blood pressure stabilized in another twenty-four hours and the medication was discontinued. Seven days later a shock-like state suddenly developed and the patient died. The skin discoloration and vesiculation had become worse in the interim.

CASE III. H. G., a sixty-eight year old white man, was hospitalized on February 4, 1955, because of a chronic cough and hemoptysis. Immediately following a bronchoscopic procedure several days later, a shock-like picture developed with a marked drop in blood pressure. Norepinephrine (4 mg. in 1,000 cc. of 5 per cent glucose solution) was administered by venipuncture in the right cubital vein for twenty-four hours. Two days later a bluish discolored area about 5 by 6 cm. was noted in the cubital area at the site of the previous infusion. This area slowly demarcated and sloughed, and was later covered successfully by a split-thickness skin graft.

CASE IV. F. D., a fifty-four year old Negro woman, was hospitalized on December 7, 1954, in a state of shock due to bowel obstruction of four days' duration because of an incarcerated large ventral hernia. She was known to have severe polycythemia vera which had been controlled by venesection. On admission the blood pressure was 90/50 compared to a usual pressure of 190 to 200/110. Norepinephrine (4 gm.) was added to each of two 1,000 cc. infusions of 5 per cent glucose in water and saline which were administered via cannulization of the left saphenous vein at the ankle. When the patient was hydrated the hernia was successfully reduced surgically. It was necessary to continue norepinephrine infusion for several days. On the second postoperative day

FIG. 3. Case v. Cyanosis and bleb formation at the site of infiltration of norepinephrine solution.

subcutaneous infiltration of the infusate was noted at the point of cannulation. The infusion was discontinued at that site and reinstituted into a forearm vein where it was necessary to maintain it for only another twelve hours. On the third postoperative day an extensive area of discoloration developed along the course of the saphenous vein in the left leg and thigh. (Figs. 1 and 2.) In this area large blebs eventually developed which contained a clear yellow fluid. The extensive area demarcated and was eventually débrided and covered with a split-thickness skin graft. The total hospital stay was two and a half months.

CASE V. H. S., a fifty-three year old white woman, was hospitalized on March 2, 1955, because of fainting, memory lapses, weakness and personality changes. Physical examination and ventriculography established a diagnosis of left frontal lobe tumor. At operation a left frontal lobe cyst was evacuated and part of its wall resected. Because of a marked postoperative drop in blood pressure, apparently not due to loss of blood, norepinephrine (4 mg. per 1,000 cc. of 5 per cent glucose solution) was administered into the left foot by venipuncture. Although the norepinephrine was discontinued in twenty-four hours, a 10 by 6 cm. irregular area of skin, mostly proximal but in a small area also distal to the venipuncture, became cyanotic and vesiculated within forty-eight hours from the start of administration. (Fig. 3.) The patient died one week after craniotomy during which time the involved skin and subcutaneous tissue became definitely gangrenous.

CASE VI. R. K., a forty-seven year old white man, was given insulin shock therapy for schizophrenia in the Psychiatric Unit of the Michael Reese Hospital. On one occasion circulatory collapse developed after he vomited a postshock feeding. Norepinephrine (16 mg. in 1,000 cc. of 5 per cent glucose solution) was necessary to maintain his blood pressure and was administered via a cannula inserted into the saphenous vein for two days; it was then discontinued. At that time an area of purplish discoloration was noted in the skin of the calf proximal to the point of the cannula. Eventually an area of skin measuring 1 by 2 cm. sloughed out in the center of this area. The area epithelized spontaneously over a period of several weeks.

COMMENTS

Kurkland[6] believes that leakage of the solution around the intravenous needle and infiltration into the surrounding tissue causes the vasoconstriction and tissue necrosis. He suggests the application of local warm compresses to prevent the complication. Greenwald[5] suggests that the infusion be given through a polyethylene catheter inserted high into the vein to prevent the leakage. However Kepes, Haimovici and Marcus[7] reported three cases in which skin gangrene developed in the calf below the knee well above the point of insertion of a Horsley cannula at the ankle. They believe that there is spasm of the infused vein with stagnation of the solution, and that some of the solution may be forced into the collateral venules, thus reaching the capillaries and arterioles, to cause the profound ischemia and tissue necrosis.

It seems to us also that both local infiltration (Fig. 3) and stagnation of the norepinephrine solution in the vein (Fig. 1) may result in skin

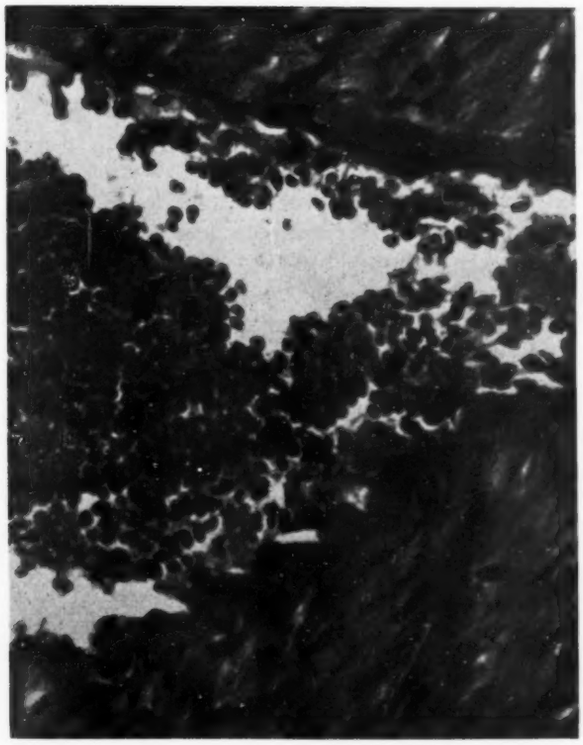

FIG. 4. Photomicrograph of section of perivenous tissue before filling the vein with norepinephrine solution. The vessels are dilated and filled with blood.

FIG. 5. Photomicrograph of section of subcutaneous tissue fifteen minutes after local infiltration with nor-epinephrine solution. There is marked vasoconstriction and emptying of the vessels.

necrosis. In the latter instance diffusion of the solution through the vein wall would offer an explanation for the involvement of the tissue along its course.

In order to determine whether such was the case and to study the mechanism, several experiments were undertaken. A 2 inch segment of a canine femoral vein was isolated by ligatures and allowed to remain in approximately normal relation to the surrounding structures. An aqueous solution of methylene blue was then introduced into this segment. Within ten to fifteen minutes the surrounding tissues became blue-stained, indicating visibly perfusion of the dye through the vein wall. In another similar vein preparation, norepinephrine solution of the usual concentration used clinically was introduced. Biopsy specimens from the surrounding tissues were taken before and fifteen minutes after the introduction of nor-epinephrine solution for microscopic examination. At the same time small subcutaneous injections of saline solution and of norepinephrine solution were made at a distance from the vein preparation. Biopsy specimens for study were also taken from these two areas after fifteen minutes.

Microscopic examination of the biopsy specimens revealed no abnormal changes in the dermal blood vessels after the formation of a saline wheal and normal vessels in the perivenous tissues before the introduction of nor-epinephrine solution into the vein segment. (Fig. 4.) Subcutaneous injection of nor-epinephrine solution caused thickening of the walls of the small dermal vessels and partial to complete emptying of their lumens. (Fig. 5.) The perivenous tissue obtained fifteen minutes after the introduction of norepinephrine into the isolated vein segment revealed similar changes but in a lesser degree. (Fig. 6.)

These studies indicate that perfusion of nor-epinephrine solution through an undamaged vein wall is conceivable under conditions of sluggish circulation and stagnation of the blood within the veins which are usually present in shock-like states. A factor which may intensify such stagnation of the blood is the acute spasm of the vein which so commonly occurs after the first rapid influx of the norepinephrine solu-

FIG. 6. Photomicrograph of section of perivenous tissue fifteen minutes after filling a segment of vein *in situ* with norepinephrine solution. Vasoconstriction and emptying of the vessel is noted.

tion. We have observed that often after a technically satisfactory cannulization of a saphenous vein the flow stops after the infusion of the first few cubic centimeters of the pressor solution. Injection of a small amount of a non-pressor solution will overcome the obstruction and reinstitute the flow. If the clinician is not aware of this phenomenon he may make injudicious manipulations which can only increase the liklihood of perivascular infusion of the pressor solution. A solution without norepinephrine is advisable until the cannulization is complete and functioning satisfactorily, after which transfer to the pressor solution may be made. This will also preclude the possibility of subcutaneous infiltration of the pressor solution while the cannulization is being performed. If venous spasm does occur subsequently the flow should be slowed and patience exercised. Application of warm compresses along the course of the vein and injection of a small amount of procaine into the tubing may be helpful. Insertion of a cannula, or whenever possible a fine polyethylene catheter, high into the vein of the extremity where the flow is more rapid than in the peripheral vessels and where the solution is quickly diluted by the larger volume of blood, and elevation of the extremity to aid in venous return should prevent necrosis due to stasis of the solution in the vein. When norepinephrine solution is required only intermittently, and if the catheter is kept in the vein for immediate availability, it would be advisable to flush out the vein with saline via a three-way stopcock in the intravenous system to prevent stagnation of the norepinephrine solution in the vein.

SUMMARY

Six cases of skin necrosis following intravenous use of norepinephrine are reported. The mechanisms of the development of this complication and some methods to prevent it are discussed.

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Dating the Onset of Dupuytren's Contracture

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IN my clinical experience and reading regarding sclerosis of the palmar fascia, I have never known of a case in which the actual onset was a matter of record rather than a more or less distant memory. Even if the patient is intelligent and observant, his response to inquiry concerning date of onset is very vague; and often his fingers have reached the contracture stage before medical advice is sought. The most authentic dating of the actual onset, insofar as my own experience is concerned, is the following case:

The patient (the author) had a previous history which was unrelated to his condition except that his father, a doctor, had Dupuytren's contracture in his left hand, which showed rigid bands and minor contractures of the fourth and fifth fingers.

Onset of the ailment in the left hand was said to be on June 1, 1953, at which time the following observations were made: "Quite by chance noted nodular soft oval swellings about three-fourths of an inch in diameter at the palmar interspaces between the left fourth and fifth fingers. At the base of the ring finger and running upward for about one inch there was a rigid band about one-eighth of an inch wide. There was also a similar band at the palmar interspace of the left thumb."

It was observed that extension of the ring finger caused a marked wrinkling of the ulnar border of the involved palm. There was no pain on pressure over any portion of the hand and function was unimpaired throughout all of the extremity. The patient, who is right-handed, had never had any injury to either hand and had not done any continued or prolonged manual work.

Within a few months it was noted that the right hand was becoming affected to a lesser degree and that extension of the ring finger caused wrinkling of the ulnar border of this palm. I have noticed and called attention to this test,[1] which apparently denotes adhesions of the underlying fascia in early or established cases. Curiously, there are periods when the condition appears to have receded or to have advanced, or it remains unchanged. In November, 1954, one of the very rare manifestations of this condition appeared, namely, a cupping instead of a transverse ridging over the middle knuckle of the middle finger of the left hand. Extension of this digit also showed the dimpling clearly. I have shown my hands to many professional friends, and have had the unusual experience of finding in some a positive response to the palm-wrinkling test already mentioned. This again shows how the disease process may be well advanced without the patient becoming aware of it, as many writers have noted.

This, then, is the report of an established bilateral case of Dupuytren's contracture which has the unusual features of showing in the rarer forms at the base of the thumb and over the middle knuckle of the more involved hand. There is no doubt that this process had been present five years or more before being recognized.

Reasons for this lack of awareness are: (1) there is no pain; and (2) there are periods when the lumps (nodules) and the ridges (fascial bands) apparently disappear and no heed is taken until a detailed examination is made or contractures become noticeably annoying. An odd factor is that no disability occurs until manual facility lessens because of bent fingers. However, this manifestation is frequently long-postponed because the patient, often without realizing it, adapts to the limitation of function.

My own belief is that heredity and the onset of sclerotic processes are the only factors that occur often enough to stand in etiologic relationship. As is well known, the condition usually appears in patients between forty and

fifty years of age, although there are a few reported cases in which the contracture was noted in patients decades younger; formerly injury or infection of the hand was regarded as sufficient proof of the time of onset. That idea, however, has been discarded by most experienced observers as have so many other alleged sources. The opinion is still maintained by some that repeated trauma to the palm in the patient who is predisposed to the condition is an element that may bear responsibility. This theory of predisposition can be assumed in a great variety of diseases, and that may be one reason why rheumatism, arthritis and gout were supposedly factors as indicated long ago by a group of writers. Recently coronary lesions have been added as suspects; indeed, so many theories of origin have been and are maintained that the riddle is no nearer solution now than it was in 1831 when Dupuytren's name was given to the disease. The puzzle is the more remarkable because the anatomy, pathology, age incidence, site and symptoms have been unchanged since attention was first called to Dupuytren's contracture. My own recent observation that may have some bearing on the ring finger selectivity of the initial sclerosis is that this digit is the only one that has a double nerve supply, median and ulnar. In like manner, this same neural distinction applies in the foot respecting the internal and external plantar nerves in the rare cases of this disease on the sole.

It is hard to understand how repeated trauma or predisposition can apply to an ailment that appears without notice, progresses of itself leisurely or rapidly, has periods of advancement or recession and almost always affects the least used part of the hand. Also, this contracture occurs in manual workers less often than in non-manual workers, and is rare in women and many races. It is painless in an area highly responsive to irritation, inflammation or infection, is exceedingly rare and may escape notice in the early stages unless special tests are applied. It is no respecter of persons when the half-century age period is imminent. It appears with great regularity in the region of the palmar base of the fourth or fifth fingers, never following injury or infection of the sensitive palm. Almost the only disregarded affection of the hand, it may be ascribed to an unrelated source if noticed in a period of activity and go unobserved when quiescent. Like gray hair, baldness and wrinkles, it is an age index and may have unexplainable familial and hereditary origins. As an etiologic factor, predisposition sounds more like theory than fact and covers a lot of disputed territory like many of the reputed sources advanced for over a century.

In summary, I, as the patient, have an ailment which has clinically interested me for almost half a century,[2] yet which I did not recognize—a condition that has now become readily apparent. Indeed, I would not have discovered the condition if I had not again and again examined my own hands, trying to fathom the mystery of the predilection for the fourth and fifth fingers and the pinpointing of the pattern in so definite a section of the palm. The birth of this ailment may be in retribution for many years of vain search for the actual parentage of the ailment in others. It may also be guilt by association; however, this recording has at least the merit of self-discovery and careful nurture and observation for two and a half years. It is also another instance of heredity, but my lack of awareness cannot be charged to my forebears.

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SURGICAL REVIEW

Fracture of the Spine

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Fracture of the spine may occur in the cervical, thoracic or lumbar vertebrae, or in the sacrum or coccyx. It may involve the body of the vertebra, a pedicle, articular process, transverse process, lamina or the spinous process. There is often associated injury to the ligaments, sometimes to the intervertebral disc. The spinal cord, the cauda equina or the nerve roots likewise may be injured. At times the muscles running alongside the spine or important blood vessels adjacent to the vertebral column are damaged. Dislocation or subluxation of the spine may occur without fracture, but is often associated with fracture, especially in the cervical region. This article is limited to a discussion of fracture of the thoracic or lumbar spine without significant spinal cord injury. It is based upon studies of 200 patients seen in the years 1920 to 1950, with a follow-up of one to thirty years (average, seven and a half years).

Types of Fractures. The most common fracture in the thoracic and lumbar spine is compression fracture of a vertebral body. The twelfth thoracic and the two upper lumbar bodies are most frequently affected. Such fractures may be single or multiple. Multiple compression fractures are usually contiguous but this is not always the case. Next in frequency in the lumbar region is fracture of a transverse process, often multiple, sometimes associated with fracture of a vertebral body. Fracture of one or both pedicles is rarely recognized and probably rarely occurs. Fracture of an articular process, lamina or spinous process is more common but is not always recognized. Such a fracture may be associated with fracture of a vertebral body. Dislocation or subluxation of the lateral articulations, sometimes of the vertebral bodies, is not uncommon with moderate or severe compression fractures and is more frequent with lateral wedging or comminution.

Etiology. Compression fracture of a vertebral body results from forcible flexion of the spine, usually sudden. This can be caused by a fall from a height onto the feet or buttocks while the trunk is in the flexed position, a fall on the head and shoulders while the spine is flexed, or a heavy blow on the head and shoulders. Lateral wedging is associated with a rotation or lateral bend injury as well as flexion. If a person falls from a height onto the feet, there may be an associated fracture of the calcaneus, rarely of the femur or tibia.

Compression fracture of the vertebral body may be seen at any age but is uncommon in childhood and rare below the age of ten years. It is common in elderly people, especially women, with osteoporosis of the spine; several such fractures may occur in succession. Similarly, compression fracture (sometimes multiple) is often associated with bone destruction due to metastatic carcinoma in the vertebral body. Such fractures may occur with trivial injury or no recognizable injury. On the contrary, fracture of the vertebral body associated with osteomyelitis is rare. Compression fracture caused by shock therapy in psychiatric patients is more common in the thoracic region.

Pathology. Compression fracture of a vertebral body commonly occurs in the cancellus bone of the proximal half of the vertebra above the pedicle. The fracture is usually transverse, although there may be an associated vertical

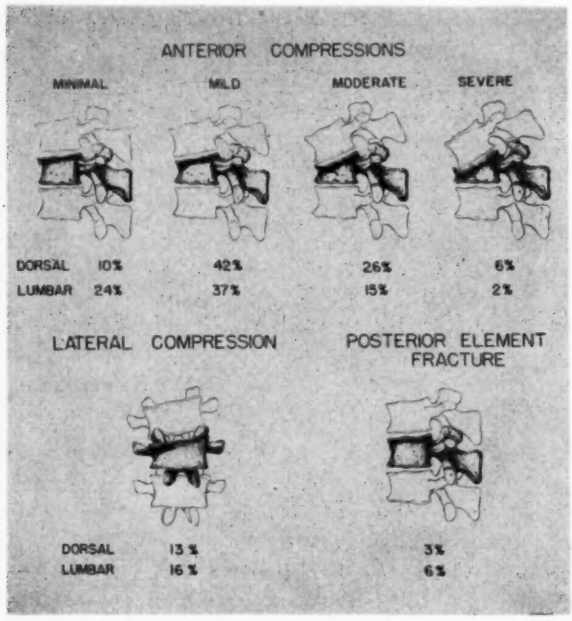

FIG. 1. Compression fracture of the spine; classification and grouping according to frequency of various types. (From: Howworth, M. B. Textbook of Orthopedics. Philadelphia, 1952. W. B. Saunders Co.)

fracture. Comminution is not uncommon. Usually the compression is bilaterally symmetric, but sometimes is more to one side. (Fig. 1.) Lateral wedging is commonly associated with injury to the lateral articulation on the wedged side with fracture of the transverse process and injury to the quadratus lumborum and psoas muscles on the convex side. Moderate or severe wedging is often associated with forward subluxation and tear of the interspinous ligament; there is also subluxation or dislocation of the articular facets with or without fracture of an articular process. Lateral displacement is sometimes present. The facets are usually locked when they are dislocated forward or laterally. Usually the superior plate does not appear to be broken but there may be a fracture of the superior plate with or without a transverse fracture through the cancellus bone. The intervertebral disk may rupture into the body through the fracture in the superior plate. Sometimes there is a fracture of the posterior surface, as if the vertebral body had exploded. This latter type of fracture may cause spinal cord pressure, early or late. Fracture confined to the inferior half of the body with or without involvement of the inferior plate is rare. However, vertical fractures commonly extend throughout the vertical height of the body and involve both superior and inferior plates as well as the adjacent disks. Comminution, often with considerable separation of fragments, is frequent with fractures of this type.

Rupture of any or several of the intervertebral ligaments may be associated with compression fracture of the vertebral body, but is more commonly associated with fractures of one or more of the processes. Such ruptures may be extensive enough to result in instability between the vertebrae, which may be seen at open operation. The interspinous ligament is usually torn with subluxation or dislocation of the lateral articulations. The intervertebral disk is ruptured with fractures through the superior or inferior plates and with subluxations of the vertebral bodies. A portion of the disk substance may extrude or be forced into the vertebral body. The ligamenta flava, ligaments of the lateral articulations, and the anterior and posterior longitudinal ligaments are torn with complete dislocations. Such injury is often associated with damage to the spinal cord or nerve roots. There may be considerable hemorrhage in the vicinity of the fracture followed by edema and fragility of the surrounding soft tissues. In the lumbar region the hemorrhage may follow the sheath of the psoas major muscle. Intradural hemorrhage may cause serious damage to the spinal cord.

CLINICAL FEATURES

Symptoms. The symptoms of fracture of the thoracic or lumbar vertebrae are pain in the back (usually localized), stiffness, weakness and disability. The intensity of the symptoms varies with the severity of the injury and the interval since injury. There may be additional pain, sensory disturbances or paralysis due to injury to the spinal cord or nerve roots. The disability may be slight, moderate or extreme.

Physical Examination. Physical examination often reveals an angular kyphosis at the site of fracture. This is less obvious in the lumbar region because of the natural lordosis. There may be a slight tilt of the spine to one side, indicating an asymmetric fracture, in which case there is usually a gentle compensatory scoliosis. Motions of the spine, especially in the region of the fracture, are limited by pain and muscle spasm. In lumbar fractures hyperextension of the hips is limited by spasm or hemorrhage in the psoas muscle. In such a

case there may also be abdominal symptoms and signs. Localized deep tenderness and percussion pain over the spinous process of the affected vertebra are present. Neurologic signs are present if the spinal cord or nerve roots are damaged.

Laboratory Tests. There are no specific laboratory tests for compression fracture of the spine but the laboratory may be of assistance in differential diagnosis. In the presence of neurologic signs spinal puncture may be helpful in indicating the presence of blood in the spinal fluid or of a partial or complete block. The puncture should be done distal to the level of the fracture. Caution is advised if there is an associated head injury or even a severe spinal injury, and removal of spinal fluid should be strictly limited.

Roentgenograms. Roentgenograms of the affected area of the spine are essential if fracture is suspected. Anteroposterior and lateral views are usually taken; oblique, stereoscopic and special views are sometimes desirable. Oblique roentgenograms, usually taken at about 45 degrees, are especially helpful in locating fractures of the articular processes or the adjoining laminas or pedicles. If the patient is unable to localize pain accurately or if there has been extensive or multiple injury, it is frequently desirable to have films made of each section of the spine. As it is often difficult to demonstrate the spine clearly in roentgenograms and proper interpretation may be jeopardized, it is very important that the finished films are of very good quality. Spot films may be advisable for careful delineation and for differential diagnosis as well as for an estimate of the age of the fracture. Laminagrams are sometimes helpful.

Commonly in the lateral roentgenogram the normal vertebral body is essentially square or rectangular, whereas the fractured body is wedged anteriorly and proximally. (Figs. 2 to 5.) There may be merely a fracture of the anterosuperior corner of the body, a fracture through the superior plate causing angulation of it or a depression of the entire plate due to collapse of the underlying cancellus bone. Thinning of the disk and extrusion of the nucleus pulposus through the fracture of the superior plate into the underlying body may be indicated in the films. Fracture of the inferior plate or inferior portion of the body is quite rare. (Fig. 6.) Sometimes the vertebral

FIG. 2. There is moderate compression and wedging of the body of L1, a common and typical fracture of the spine.

body is expanded anteriorly and laterally or even posteriorly as if it had exploded on impact. (Fig. 22.) Vertical fractures extending through both superior and inferior plates are not uncommon and are often associated with comminution and displacement of fragments. (Fig. 7.) Vertebral body compression fracture is unusual in children. (Fig. 8.) Compression of both superior and inferior surfaces without comminution, often without wedging, is usually indicative of involvement with metastatic tumor. (Fig. 17.)

Fractures of the pedicles, articular processes, laminas and spinous processes are more difficult to demonstrate in the roentgenograms than fractures of the bodies, and are often missed.[17] (Fig. 9.) Sometimes these fractures cannot be seen in roentgenograms even when the fracture is visualized at the operating table. The special views described previously are often helpful. In exposing the posterior portion of the spine for spinal fusion with compression fracture of the vertebral body, associated fracture of the posterior elements has been found in 15 per cent of the cases. Fractures of the transverse processes can usually be recognized if the films are good but gas shadows may be confusing. The latter may be eliminated by the use of an enema or laxative, or the films may be repeated on the following day. Associated fractures of ribs, pelvis, skull or calcaneus should

3A 3B

FIG. 3. A, August 27, 1948. Slight wedging and compression of the anterior three-fourths of the superior plate of the body of L1, including the anterior-superior corner. Alignment of the spine is hardly disturbed. Such a fracture should heal promptly and well with any treatment. Prolonged immobilization or inactivity is not advisable. B, January 18, 1949. The same fracture five months later. Patient was treated for three months in a hyperextension jacket when ambulant, and then wore a Taylor brace for one month. There is a slight kyphos. Note thinning of disk T12-L1. The fracture is well healed, with slight increase in deformity. The clinical result was good.

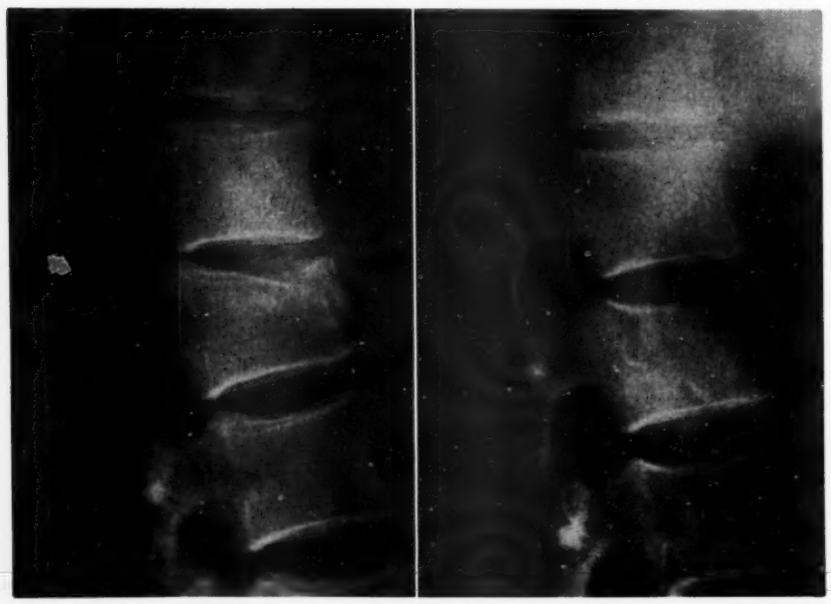

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FIG. 4. A, July 19, 1944. Slight wedging and compression of the superior plate of the body of L1. The anterior-superior portion of the body has been fractured as a free triangular fragment. This fracture extends into the disk. B, January 17, 1950. The same fracture five and a half years later. Correction was lost. There is a moderate kyphos. Fracture is well healed, with no calcifications, but slight osteoarthritic lipping. The disk T12-L1 is moderately thinned. The clinical result was good. (From: Howorth, M. B. Textbook of Orthopedics. Philadelphia, 1952. W. B. Saunders Co.)

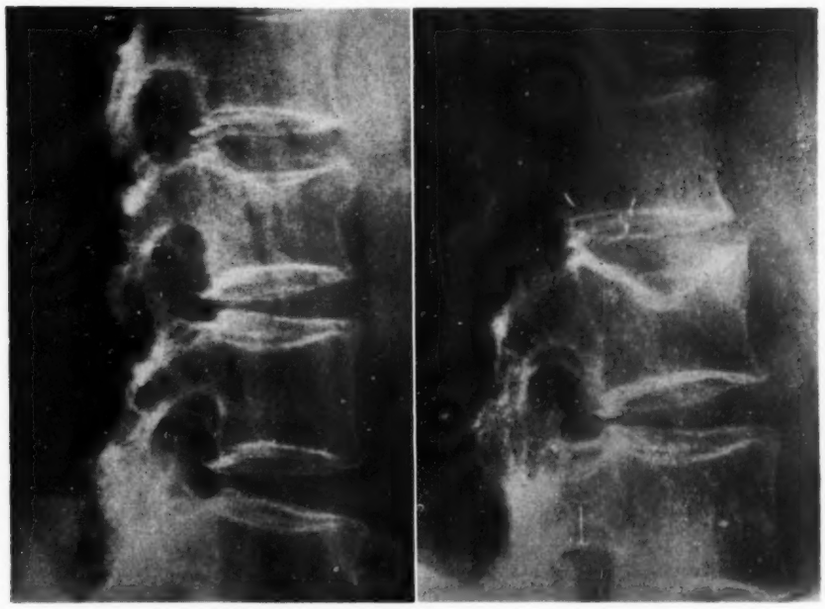

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FIG. 5. A, March 11, 1944. Fracture through the middle of the superior plate of the body of L1, with a shearing off of the anterior-superior corner. The disk is ruptured. Compression and wedging are slight. B, December 11, 1944. The same fracture nine months later. The fracture is well healed, but the disk has partly extruded into the center of the superior portion of the body and the disk is thinner. The patient wore a hyperextension jacket for three months when ambulant, and then a brace for one month. The wedging of the body is unchanged. The clinical result was good. (From: Howorth, M. B. Textbook of Orthopedics. Philadelphia, 1952. W. B. Saunders Co.)

not be overlooked. Dislocation of the lateral articulations may be recognized in the lateral roentgenogram by enlargement of the intervertebral foramen, displacement of the articular processes, disalignment of the bodies and separation of the spinous processes; in the anteroposterior view by lateral angulation and lateral compression, lateral displacement of the spinous process above, and widening of the space between spinous processes and laminas above and below.

Compression of the spinal cord is not distinguishable in the roentgenograms except possibly with the injection of an opaque substance into the spinal canal. Such injections may increase the risk of damage to the spinal cord and cause discomfort to the patient with little likelihood of really useful additional information.

The effect of treatment and the course of healing of the fracture should be followed in the roentgenogram. If the fracture is fresh and the films clear, the fracture line can generally be seen. However, because of the compression, the fracture may be seen as a line of increased density. Later the process of healing is seen in serial roentgenograms and is of assistance in estimating the age of the fracture. Callus is rarely seen beyond the normal outlines of the

FIG. 6. Moderate compression and wedging of the inferior half of the body of L1, without involvement of the superior half. This type of fracture is rare. There is a moderate kyphos.

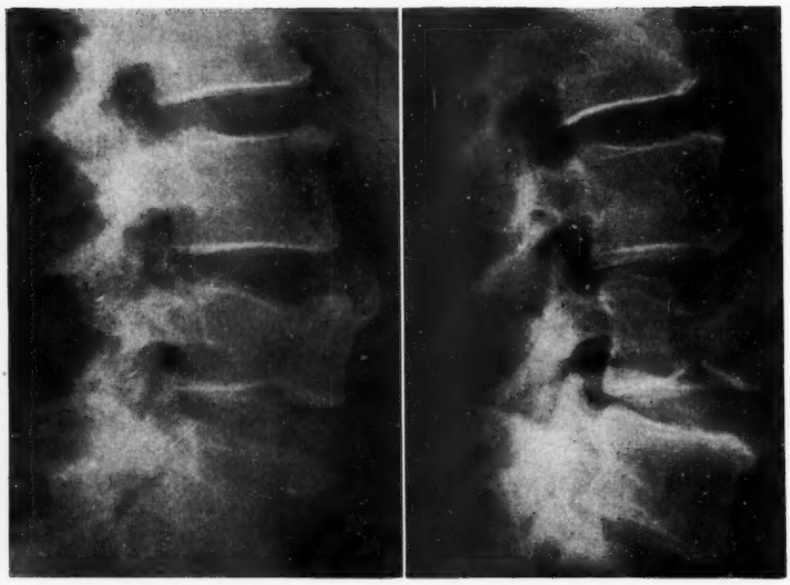

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FIG. 7. A, April 28, 1938. A comminuted vertical fracture through the body of L4, involving both plates and both disks. There is little compression but moderate anterior displacement of the anterior half. The disks are thin posteriorly. There is osteoarthritic lipping of the bodies of L3-5 and post-traumatic calcification in the anterior ligament L3-4. Hyperextension had no effect on the deformity. Patient wore a hyperextension jacket for four months when ambulant. B, ten months later, March 7, 1939, persistent pain and disability were present. Probably a better result would have been obtained in a shorter time with early spinal fusion. (From: Howorth, M. B. Textbook of Orthopedics. Philadelphia, 1952. W. B. Saunders Co.)

body. It should be realized in judging the effects of procedures to correct the compression or wedging of a vertebral body that most or all of the "correction" obtained in most cases occurs through the disks rather than the fractured body itself, and this "correction" will be lost as soon as the support is removed. There is rarely significant change in the basic height and shape of the body after the fracture. Compression fractures always heal in a few months, although the deformity persists and osteoarthritic changes may supervene. Calcifications are common when hemorrhage has occurred in the ligaments of the spine, especially anteriorly.

Diagnosis. The diagnosis of compression fracture of a vertebral body is not difficult in typical circumstances, but may be quite difficult under other conditions.[10] The diagnosis may be less certain when there has been no recent injury and no fracture line is seen, and when there is a deformity which might represent a fracture but which could well be due to some other cause. Sometimes there is no doubt that the vertebral body is compressed, but the etiology may be obscure. Sometimes the diagnosis of compression fracture is definite enough, but there are associated lesions of the spine, e.g. osteoarthritis (Fig. 22), and it may be necessary to attempt to assess the importance of each lesion in the production of symptoms and disability. This is especially likely to be the case when compensation or liability is involved.

A wedge-shaped vertebral body may be the result of congenital deformity. The wedging may be either anterior or lateral. The common congenital deformity producing lateral wedging, and often some deficiency in development of the body, is hemivertebra, of which there are several varieties or degrees. Hemivertebra is often multiple, sometimes on the same side, sometimes on both sides. (Fig. 10.) In the thoracic region, hemivertebra is often associated with congenital deformities or asymmetries of the ribs. Congenital failure of segmentation of vertebral bodies may also be mistaken for a post-traumatic condition. One variety of such deformity, called the Klippel-

Feil syndrome, is seen in the cervical spine, the vertebral bodies being malformed and often joined together. A persistent or accessory ossification center, occurring usually anteriorly and cephalad, may be mistaken for a fracture of the anterior corner of the body. (Fig. 23.) Deformities of the vertebral bodies are also characteristic of several of the chondrodystrophies. Spondylolysis is characterized by a separation of the pedicle of the vertebra from the articular processes. This is commonly bilateral, sometimes unilateral. Separation of the two portions of the vertebra at this point results in a forward displacement of the portion made up of the body and the pedicles, called spondylolisthesis. (Fig. 11.) The consensus of present opinion is that this lesion is not due to a fracture and that it develops in childhood. Absence of a portion or all of the spinous process, sometimes associated with partial or complete absence of the laminas is not uncommon, especially in the lumbosacral region. This defect, called spina bifida, sometimes involves several vertebrae and a portion or all of the sacrum. It is seen less often in the cervical and thoracic regions.

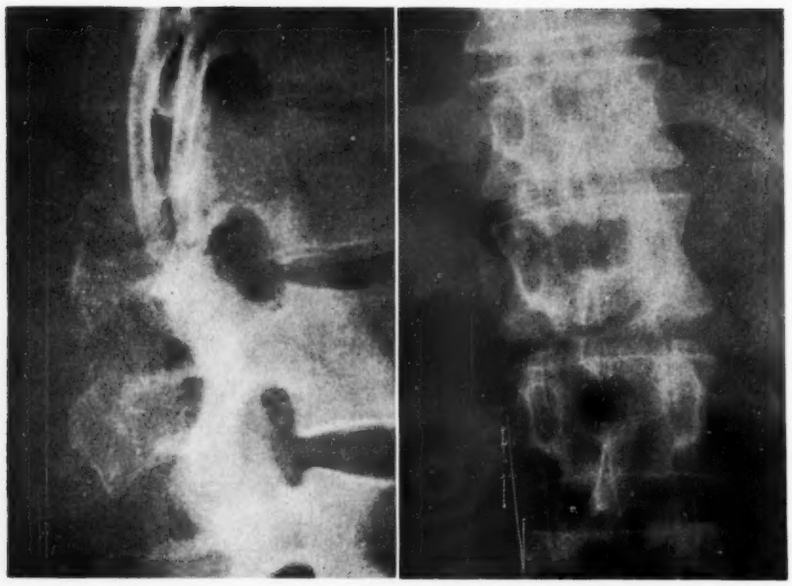
Fracture of the spine is uncommon in children. Roundback, a structural deformity due to irregular wedging of one or more of the vertebral bodies in the thoracic region, with the exception of poor posture, is probably the most common disease of the spine in childhood. (Fig. 12.) It can usually be distinguished without difficulty by the double wedging of each affected body, the irregularity of the superior and inferior plates, and the lack of a fracture line. The somewhat similar wedging of the vertebral bodies may be seen in elderly people, accompanied by thinning of the disks, osteoporosis and frequently osteoarthritis. This deformity is seen much more often in women than in men. However, single or multiple compression fractures of the affected vertebrae are common in this group, especially in the thoracic region. (Figs. 21 and 22.)

Tuberculosis of the spine commonly results in anterior wedging of one or more of the bodies but is characterized by destruction of bone rather than fracture. (Fig. 13.) Furthermore, the intervertebral disks are commonly destroyed; this is more conspicious earlier in the disease than wedging of the body. The globular shadow of the paraspinal abscess may also be seen in the roentgenograms. Other infections such as osteomyelitis of the spine are less likely to be confused with simple fracture. (Figs. 14 and 15.)

FIG. 8. The lumbar spine of a ten year old boy. There is moderate compression of the superior portion of the body of L4 and slight compression of the inferior portion. Thus, there are two simultaneous fractures of this body, also rare. A slight superior compression of the body of L3 also is present. The disks have expanded anteriorly sufficiently to prevent a kyphos. Such fractures in children usually heal promptly with protection for two to three months, with good clinical results.

Osteoarthritis can usually be distinguished from fracture of the spine without difficulty, although the two are sometimes associated. However, it may be more difficult to distinguish the spur formation of osteoarthritis from the calcifications occurring after a fracture. In fact, probably one of the common causes of localized osteoarthritis of the spine is traumatism.

Benign tumors of the spine are rare. Fracture could occur in a giant cell tumor of a vertebral body, resulting in a problem in differential diagnosis. Malignant tumor, usually metastatic in origin, involves vertebral bodies all too often, and may result in spontaneous fracture. (Fig. 16.) Recognition of the fracture is usually not difficult but recognition of the tumor is not always easy. Sometimes the first evidence of malignancy in the patient is the pathologic fracture in the vertebral body. Metastatic spinal lesions commonly arise from carcinoma of the breast or the prostate, and occasionally from the thyroid, kidney or bronchus. It may be necessary to consider multiple myeloma or



9A 9B

FIG. 9. Anteroposterior (A) and lateral (B) views. Transverse fracture through the spinous process and the laminas of L1, with slight separation of the fragments. At operation a fracture of an inferior articular process into the facet was found and there was considerable instability. A spinal fusion was done, T12 to L2, and an excellent result was obtained. The patient returned to moderately heavy work in six months, without pain or disability. Such a good result would not be expected with any other treatment.

FIG. 10. Hemivertebra, L3. The vertebral body on the right side is about 50 per cent thicker than the other lumbar bodies, and there are two pedicles and transverse processes on this side, only one of each on the left. The laminas and the spinous process of this vertebra are increased in width. This is not the result of traumatism, but is a congenital fault of segmentation.

FIG. 11. Spondylolisthesis, L5. The body and pedicles of this vertebra, with the superimposed spine, have slid forward ½ inch on the body of S1, whereas the posterior elements of L5 have remained behind with the sacrum. There is a gap between the pedicles and the pars interarticularis on each side. This is not a fracture but a separation, probably on a nutritional basis. True fracture in this part of the vertebra is rare.

FIG. 12. Wedging of the inferior surface of the body of T7, with an ovoid defect anteriorly. There are similar but slight changes in the adjacent vertebral bodies. This is not a fracture but the result of a vascular disturbance in childhood, an osteochondrosis or Scheuermann's disease.

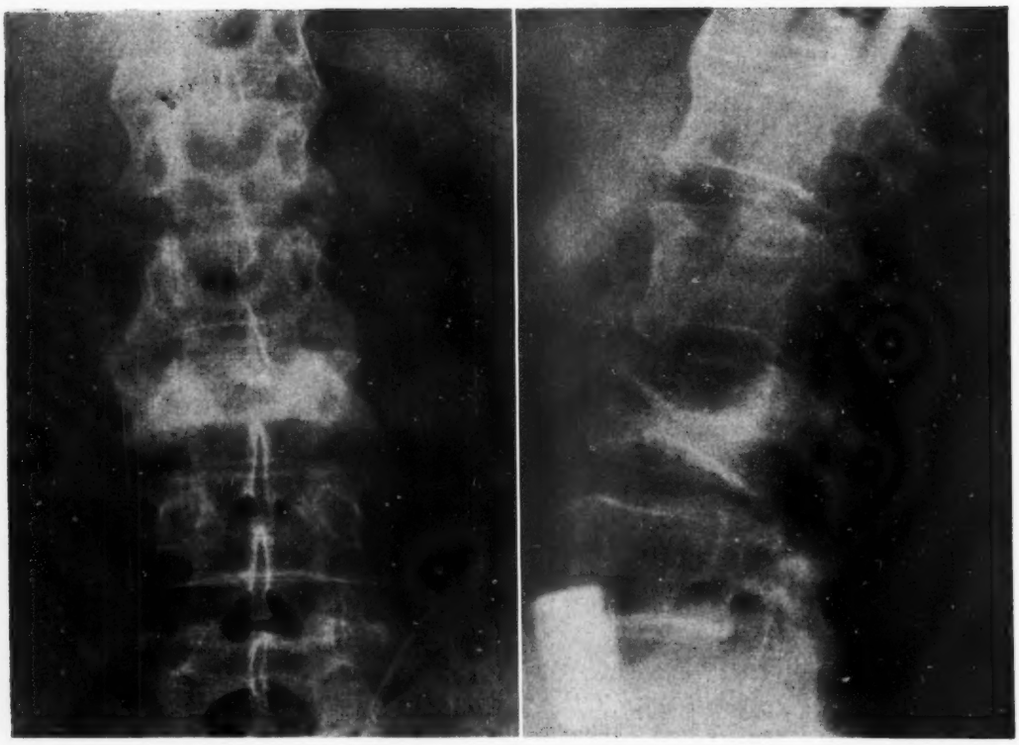
even Hodgkin's disease in differential diagnosis. (Fig. 17.)

TREATMENT

Treatment of compression fracture of a vertebral body involves not only the healing of the fracture but also correction of the deformity and the effects of soft tissue injury. Healing of a fracture of the vertebral body always occurs within a few months, regardless of treatment. (Fig. 18.) However, correction of the deformity is difficult and often impossible. Attempts to correct the deformity date back at least to ancient Egypt, Hippocrates and medieval times.[1,15] Some of our modern methods of correction resemble these ancient ones, and it appears that little more has been accomplished in modern times. The basic principle of correction of the compression fracture is hyperextension of the affected portion of the spine. However, the pull is so distributed through the various joints that hyperextension as ordinarily practiced is often not effective in producing real correction of the compression. Forceful hyperextension with localized pressure at the site of deformity, with or without anesthesia, may be more successful in producing correction, but may add risk of damage to the spinal cord.

FIG. 13. Marked wedging inferiorly of the body of L2 and almost complete disappearance of the body of L3, due to bone absorption. The disk has virtually disappeared. There is a moderate kyphos. No fracture line is seen. In the anteroposterior view the psoas shadows were swollen. These features are characteristic of spinal tuberculosis, moderately advanced. While the diagnosis is not difficult in such a late case, spinal tuberculosis in an earlier stage might easily be confused with fracture, especially if the roentgenograms are not clear.

Hyperextension may be secured with the patient in the prone position by the method of Davis.[5,7] (Fig. 19.) The arms and head are supported on a table and slings placed around the padded ankles. The feet, legs and trunk are then raised by a cord attached to the slings until the spine is completely hyperextended. The amount of hyperextension will vary with the individual, but is limited by the strong anterior longitudinal ligament. Reduction is usually accomplished by hyperextension alone, but manual pressure may be made against the kyphos if necessary. No anesthetic is used and usually a narcotic is not required. The method of Watson-Jones is similar, but hyperextension is obtained by elevating the upper trunk.[26–28] The legs and thighs are supported on one table



14A 14B

FIG. 14. A and B, moderate wedging of the body of L3, with anterior expansion, but there is also bone destruction and production. This is a pathologic fracture associated with osteomyelitis. Treatment is directed primarily at the infection.

and the head and arms on a second higher table, so that the trunk and pelvis sag between them and the spine is hyperextended. These methods are contraindicated if there is damage to the spinal cord, dislocation of the lateral articulations, fracture of the neural arch, other serious injury, or an associated spondylolisthesis or significant disease of the spine. The methods are effective for the lumbar and lower thoracic spine, less so for the remainder of the thoracic spine and inappropriate for the cervical spine. With either method a snug plaster jacket is applied from the clavicles to symphysis pubis in front; it is shorter in back and well molded, with no excess padding. While either of these methods may be suitable for persons who are young, strong, of light weight, healthy and cooperative, under other circumstances they may prove difficult, especially with women. Hyperextension on a canvas sling is more comfortable but less effective.

Hyperextension may be obtained with the patient in the supine position with a support under the spine at the level of the fracture, allowing the weight of the head and arms at one end, the pelvis and legs at the other, to produce the hyperextension. This can be accomplished simply and safely by using a bed with a hard mattress and hinged plywood fracture board, reversing the ends of the bed so that the patient's head is at the foot of the bed, and raising the knee Gatch with the fractured vertebra at the apex, allowing the head and shoulders to sag on one side of the Gatch, the pelvis and lower extremities on the other. The Gatch may be raised gradually to the limit of tolerance over a period of hours or even days, until the deformity is corrected, as seen in the lateral roentgenogram. Maximal correction will probably be obtained within a few hours. Such hyperextension may be accompanied by headache, dizziness, nausea and distention, although the latter is often a concomitant of the injury. The symptoms may be reduced by placing a small pillow under the patient's head. To be effective the hyperextension must be begun fairly promptly and maintained continuously; however, it is difficult to maintain it while the patient is turned. This method is less applicable to the upper thoracic

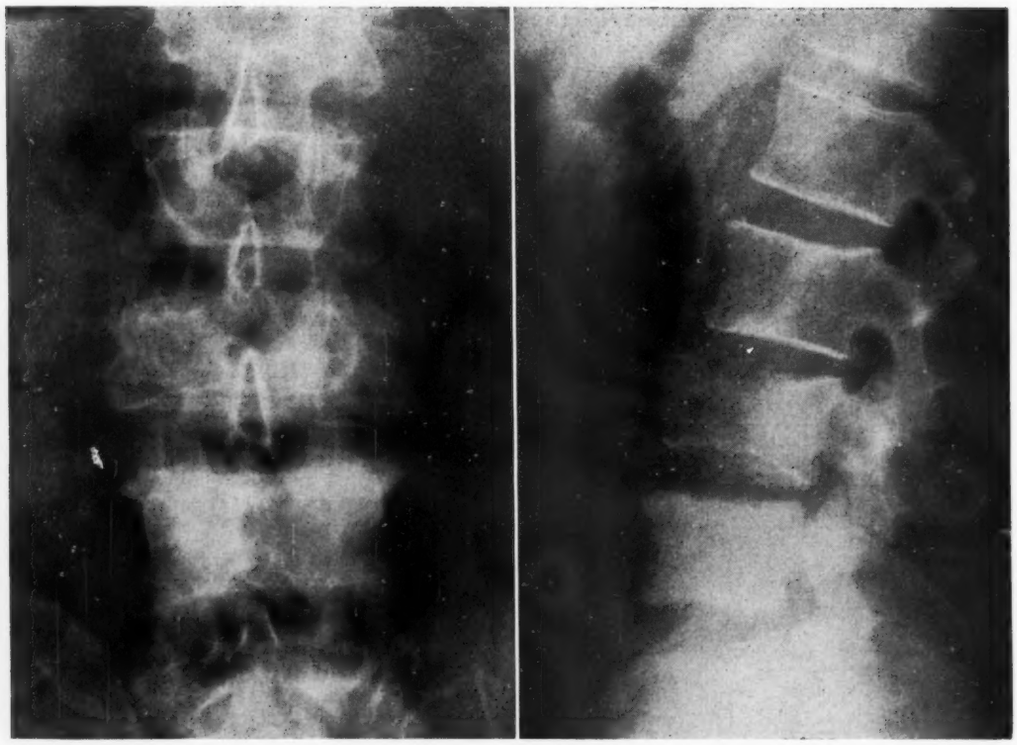
spine because of the relative fixation of the thoracic cage. Various pads[3] and hyperextension frames have been used as variations of this basic method.[21,22] The trunk may be suspended by a transverse canvas sling at the level of the fracture,[8,9,20] hyperextension again being attained by the weight of the extremities, and a plaster jacket applied. The automobile jack has been used beneath the spine as a method of correcting the kyphos, but has not met with wide acceptance, probably because of the very real danger of injury in some cases. A hyperextension plaster jacket or brace may be applied at any time during convalescence, and ambulation begun. Goldthwait irons may be used for applying the hyperextension jacket. The jacket should include the shoulder girdles if the fracture is in the upper thoracic region. These methods are more applicable to fractures in the mid- and upper thoracic region than are the prone hyperextension methods. The author is not convinced from his own experience or from what he has heard and seen in the literature that such methods are really effective in producing significant and permanent correction in most cases. Whatever the method of reduction, the use of force can be accompanied by real danger, especially if there is associated fracture of the posterior arch, rupture of the ligaments, or impending injury to spinal cord or nerve roots.

One disadvantage of plaster jacket immobilization is that it immobilizes injured soft tissues and interferes with physical therapy, resulting in limitation of motion. Furthermore, joint function, circulation and muscle activity are restricted. Prolonged hyperextension produces added strain on the lumbosacral joint, which may be followed by persistent and annoying discomfort, especially if this joint is already unstable. Extension of the jacket downward to include the thighs, with the hips in hyperextension, is more effective in maintaining reduction of the fracture by hyperextension of the pelvis and lumbar spine. However, this precludes ambulation, and may result in prolonged stiffness and discomfort in the hips and low back.

The jacket is usually worn for three to four months depending upon the location and severity of the fracture and certain personal factors. Severe comminution or extensive ligamentous injury may require a longer period for healing. The jacket may be replaced by a brace of the Taylor type for several weeks. (Fig. 20.) If the fracture is in the lower lumbar region, it is preferable to have a brace with a double pelvic bar for a firmer grip on the pelvis. If the fracture is in the upper thoracic region it is desirable to extend the brace by short curved arms across the back of the shoulder girdles, using snug shoulder straps. If no correction is obtained or correction is not desired, a brace may be used instead of a plaster jacket from the outset. A brace of the type with a light frame mounting a pad at the sternum, another at the symphysis and a wide band across the thoracolumbar region may be quite satisfactory in milder fractures.[13] No support is needed if the vertebral compression is slight in an area requiring little protection, and the patient will be in a suitable environment, is willing and able voluntarily to maintain extension of the trunk.

FIG. 15. Moderate anterior and lateral wedging of the body of L3, a pathologic fracture due to bone destruction in the middle section of the body. The superior and inferior plates are yet intact. This was a blastomycotic infection. (From: Howorth, M. B. Textbook of Orthopedics. Philadelphia, 1952. W. B. Saunders Co.)

Exercises for the muscles of the trunk and extremities are begun early and continued throughout convalescence. Exercises for the



16A 16B

FIG. 16. A and B, moderate compression and wedging of both superior and inferior surfaces of L3, with anterior expansion. The fracture extends vertically through the body and there is comminution. There was a severe injury. The body of L4 is quite dense and somewhat mottled. Aside from slight osteoarthritic lipping, it is of normal shape. This body was involved with metastatic carcinoma from the prostate, an incidental but important finding when roentgenograms were taken for the fracture.

arms and legs at least are started while the trunk is immobilized. Deep breathing is important and should be done systematically throughout convalescence. Trunk exercises, especially extension or hyperextension, are begun as soon as possible; all exercises should be done several times daily. Wall weight exercises and rowing, or their equivalent, may be employed early. After the cast is removed swimming is one of the best exercises for the trunk muscles as well as for the extremities.

Treatment of vertebral compression fracture should vary according to the location, type and severity of the fracture, the health of the spine, the age, activity and occupation of the subject and perhaps the sex, and according to the progress of the individual patient both clinically and roentgenographically. Mild fractures, especially in the upper thoracic region, which have been present for several days or weeks when the diagnosis is first made (particularly in an intelligent, cooperative patient in a protected environment) may not require support or immobilization. Minimal immobilization is advisable for fractures in elderly persons. (Figs. 21 and 22.) On the contrary, if the fracture is severe, comminuted or multiple, in the lower thoracic or lumbar region, or associated with osteoporosis, in a patient who is not dependable or who must travel or do heavy work, greater and longer protection is needed. Fractures of the posterior elements of the vertebrae also require more protection. The major problem in severe or even moderate fracture of a vertebral body is often not the fracture itself, but the soft tissue damage.[18,19] It is the damage to the joint, the disk and the ligaments which is most likely to result in persistent pain and disability. Similarly, disturbance in the alignment and mechanics of the spine may cause persistent symptoms, either at the fracture site or in the lumbosacral region. There may be sufficient damage to the intervertebral disk and its surrounding ligaments, or to the lateral articulations and their ligaments to cause pain long after the fracture has healed.

FIG. 17A. July, 1949. Slight wedging and compression of the superior and inferior plates of the body of T9 without a visible fracture through the body. Patient had a history of slight trauma, but severe persistent pain. A diagnosis of multiple myeloma was made and was confirmed by biopsy of the sternum.

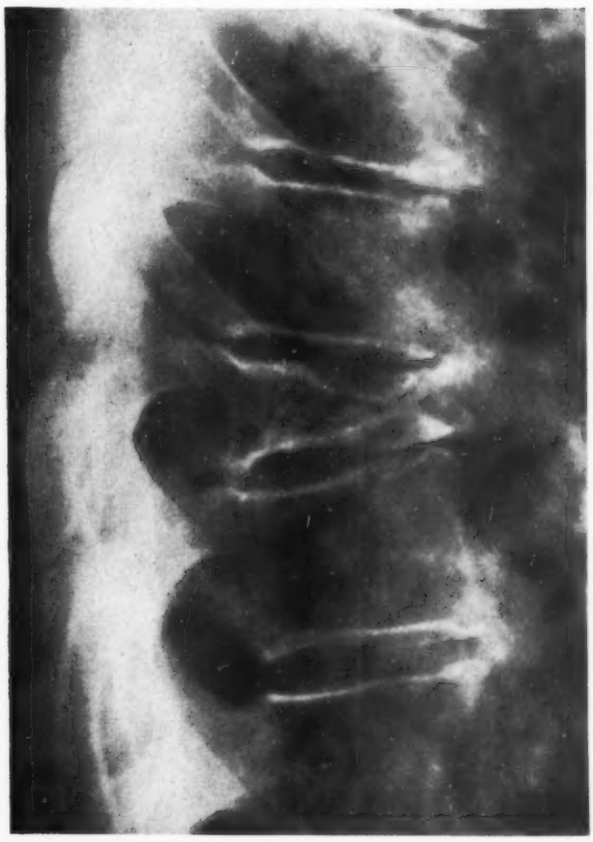
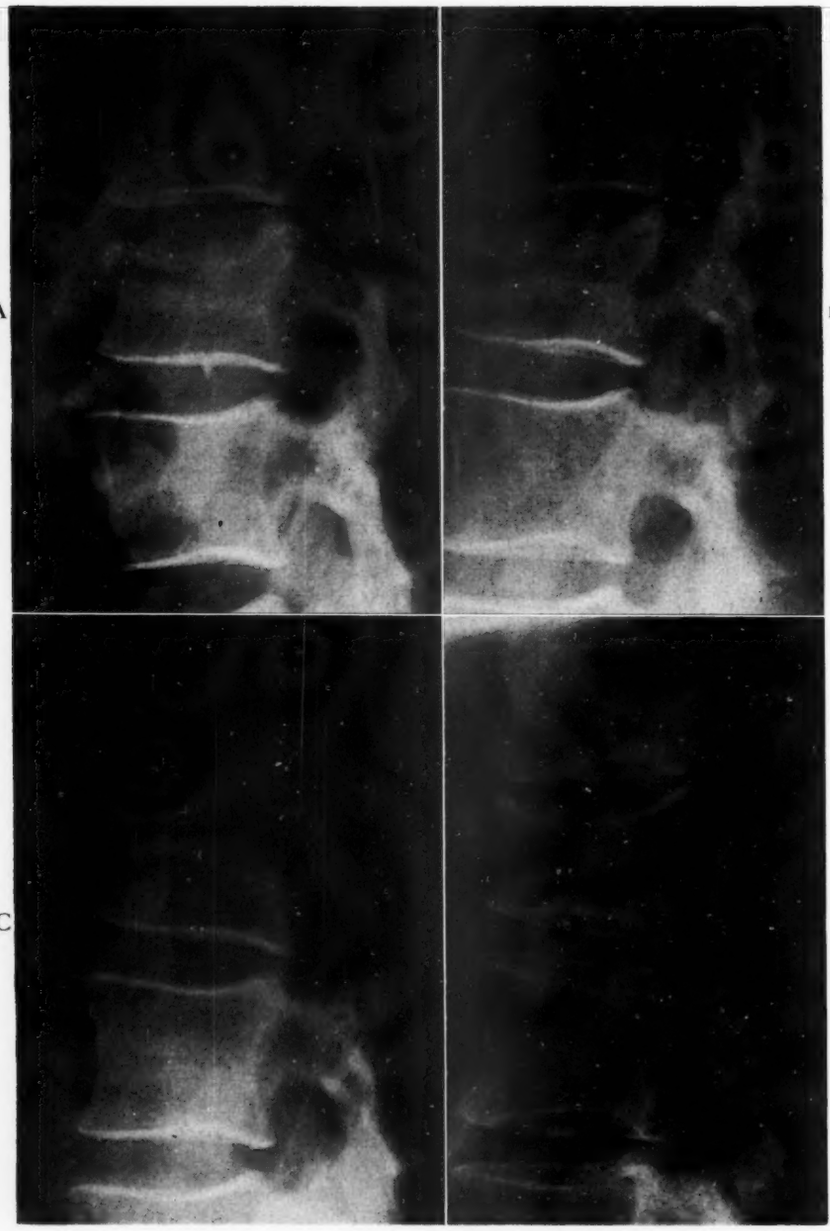


FIG. 17B. April, 1950. This is the same vertebra, nine months later, with marked compression and moderate wedging of both surfaces of the body due to bone destruction. The patient died from the tumor shortly afterward. Metastatic carcinoma causes similar changes.

An uncorrected kyphosis may result in changes in the physiologic curves of the spine in an effort to compensate for the deformity. For example, a fracture in the thoracolumbar region is often followed by an increase in the lumbar lordosis. This will not only increase the strain in the lumbar region but also pitch the lumbosacral joint forward, and is often a source of lumbosacral pain. It is of course desirable, when possible, to correct the deformity and prevent such an outcome.

When there is severe damage to a joint, especially in a person under fifty years of age who must use his back vigorously or for heavy work, spinal fusion should be considered. When spinal fusion is done, it is assumed that an orthopedist is available who is trained and experienced in this operation and its postoperative care. He should be in a position to expect fusion in a reasonable time in a high percentage of cases. Joint damage in the usual type of compression fracture is confined to the joint between the affected vertebra and the vertebra above it. Accordingly, fusion of this one joint is usually adequate. However, if there is a vertical or a comminuted fracture involving also the inferior plate, fusion of the two adjacent joints is advisable. (Figs. 23 to 25.) Similarly, if there has been an important fracture of the posterior elements of one of the vertebrae, this fractured area should be included in the fusion. (Fig. 9.) If there is a definite abnormality of the lumbosacral joint with significant disturbance in the alignment of the spine, especially if there have been previous low back symptoms of consequence, the lumbosacral joint may also be fused. It is important that the fusion area be accurately chosen. A marker roentgenogram is desirable, either just before or during the operation, except for the lumbosacral joint.

Spinal fusion is indicated for fracture of the



18A 18B 18C 18D

FIG. 18. A, February, 1954. Moderate compression and wedging of the body of T12, a common and typical fracture of the spine. Some comminution is present. No correction was obtained. A hyperextension jacket was applied, with early ambulation. B, April, 1954. The same fracture three months later after removal of the jacket. It is firmly healed, with the same deformity. The disk is moderately thinned. C, August, 1954. The same fracture six months after injury is solidly healed, with the same deformity. D, December, 1954. The same fracture twelve months after injury with mature healing. The superior surface is saucer-shaped. There is a slight kyphos. This is a typical result of the usual type of treatment. The clinical result was fairly good.

thoracic or lumbar vertebrae when there is a moderate or severe compression fracture, especially if there is significant comminution, damage to the disks or their ligaments, damage to the posterior ligaments, associated fracture of a posterior element, or if significant correction of the compression deformity has been obtained.[14,16] Spinal fusion is more clearly indicated in adults between twenty and fifty years of age who expect and desire to lead

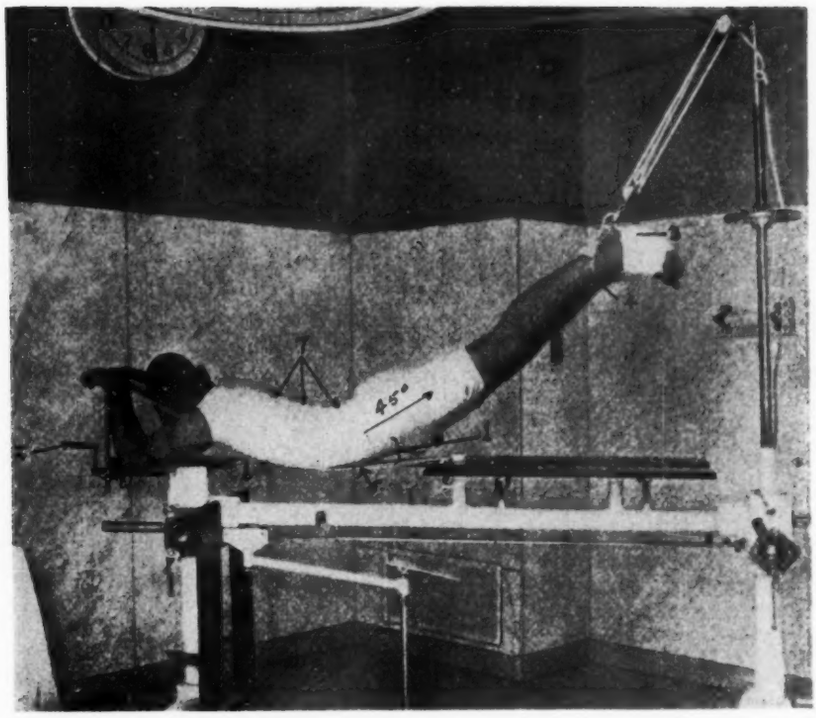


FIG. 19. The prone hyperextension method employed by Davis for obtaining correction of vertebral body compression and for application of the plaster jacket. (From: Davis, A. G. New aspects of spinal injuries. *Arch. Surg.*, 46: 619, 1943.)

physically vigorous lives or do heavy work. Fracture-dislocation is sometimes an indication for spinal fusion. Frequently, spinal fusion is also indicated in combination with a neurosurgical procedure when there has been damage to the spinal cord or nerve roots.

The postoperative care of the patient with spinal fusion for compression fracture is similar to that for fracture without spinal fusion, but convalescence is usually shorter. If correction of compression has been achieved, hyperextension is employed for maintenance of correction as previously described. A hyperextension jacket is preferable, and hyperextension exercises are begun promptly. Under suitable circumstances correction may be obtained, a jacket applied beforehand and the operation performed through a fenestration in the jacket and reinforced afterward. The time for ambulation varies with the location and severity of the fracture, the type of fusion operation and the individual patient, but is likely to be two or three weeks after operation. If there is no correction of deformity, a straight jacket may be applied and a similar regimen followed; or a Taylor brace and exercises may be used from

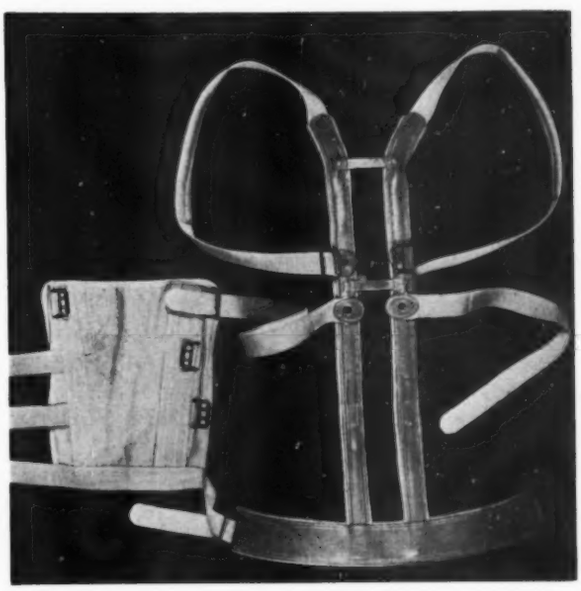
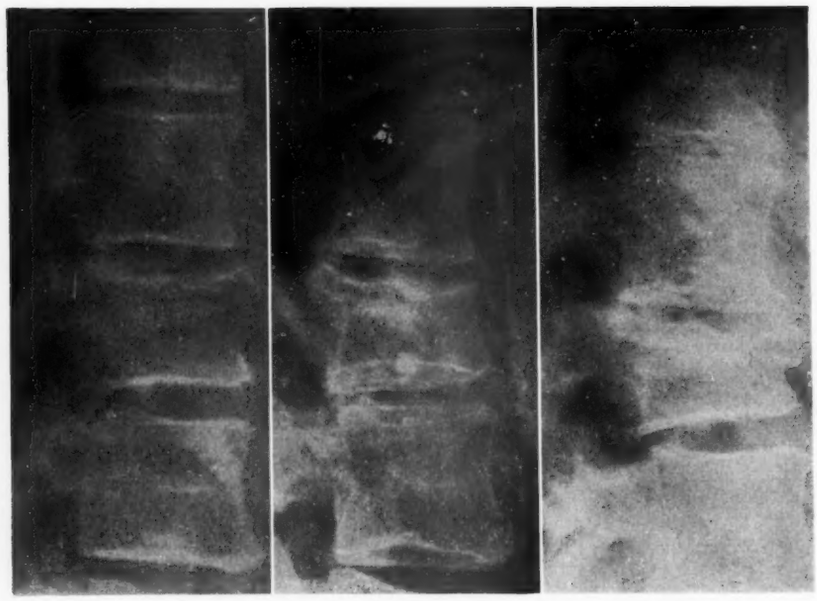


FIG. 20. Taylor brace used for support and comfort after compression fracture of vertebral body, or other fractures of the spine. The brace is used initially for mild fractures, especially those not corrected, and for elderly patients. It is used following removal of the plaster jacket in other patients.



21A 21B 21C

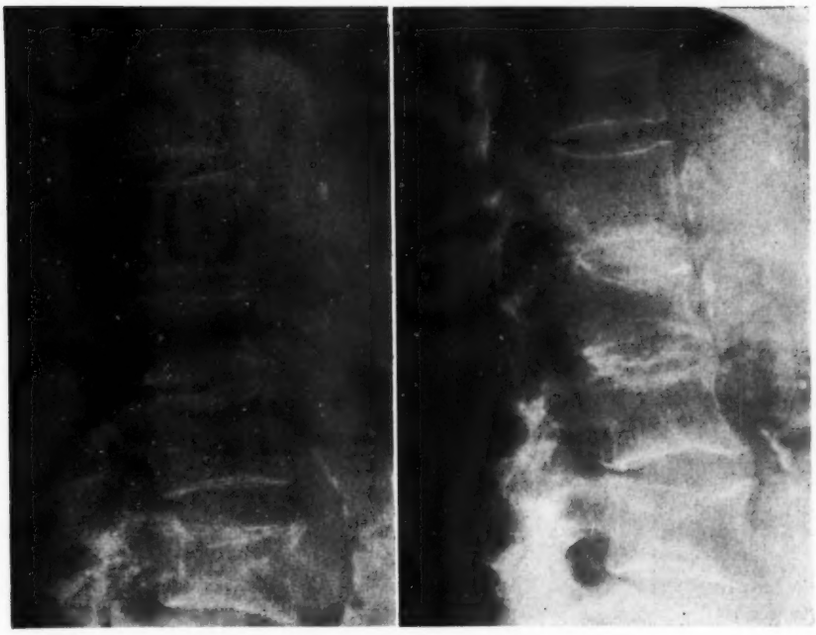
FIG. 21. A, April, 1953. Slight compression and wedging of the superior plate of L1, with a moderate anterior triangular fragment, in a sixty year old patient. Slight decalcification of the spine is present, with moderate calcification of the aorta. Reduction was not attempted. Patient wore a Taylor brace for three months. B, September, 1953. The fracture has healed, but the deformity has increased. This may be due to lack of external support, osteoporosis and vascular damage. C, December, 1953. Mature healing eight months after fracture, but the deformity has increased moderately. There is a moderate kyphos. The disk is thinned and calcifications are present anteriorly. The clinical result was fair.

the outset and bedrest continued for six weeks. If there is severe comminution or ligamentous damage, bedrest for eight to twelve weeks is usually advisable.

RESULTS

In 1951 Baab and Howorth reported the results of 125 cases of compression fracture of the dorsal and lumbar vertebrae treated by hyperextension. Reduction was obtained, when indicated, by hyperextension on a reverse Gatch bed. Hyperextension was maintained by a hyperextension jacket applied while the patient was supine on Goldthwait irons, or prone by suspension between two tables of different height by the method of Watson-Jones, or by the legs by the method of Davis. Direct pressure over the kyphos was used under anesthesia in several instances. Ambulation and hyperextension exercises were begun several days after the jacket was applied. The jacket was worn for an average of nine weeks, then usually replaced with a brace which also was worn for about nine weeks. The brace alone was used from the outset in a small portion of the cases because of age, obesity, minimal compression or lack of cooperation; symptoms persisted in these patients for a longer period after injury.

These 125 patients were followed up for an average of five years. Those with fracture in the thoracic spine returned to light work in an average of eight weeks; those with lumbar fractures averaged seventeen weeks. The average time for heavy work was ten and a half months in both groups. Slight or no residual symptoms were present in 83 per cent of the patients whereas 17 per cent had significant pain and disability. Patients with multiple fractures or with lateral compression had results which were less satisfactory than those with single anterior compressions. Only 20 per cent of those with fractures of the posterior elements in the lumbar region had good results. The greater the compression, the more severe the symptoms. However, there was a marked tendency to eventual spontaneous anterior fusion of the bodies having severe compression or com-



22A 22B

FIG. 22. A, March, 1953. Lateral view. Marked osteoporosis of the spine with slight osteoarthritis and moderate calcification of the aorta in a sixty-three year old woman. There is a slight spontaneous compression fracture of the superior surface of the body of L1. The disk at L1-2 is thinned; the contiguous surfaces of the bodies are scaphoid and irregular. There was moderate pain. No attempt at reduction was made. She was treated when ambulant with a Taylor brace, with a good clinical result. B, February, 1954. Lateral view. Appearance of spine one year later. The body of L1 has healed, but there are similar fresh fractures of T11 and L3, with recent pain. Similar treatment was employed, with a similar result.

minution, resulting in relief of symptoms after more than a year.

Correction was lost after removal of the jacket in 94 per cent of those with partial or good original correction. Possibly this percentage would have been less had the jackets been worn longer. The symptomatic results were the same whether correction was gained, lost or not obtained at all.

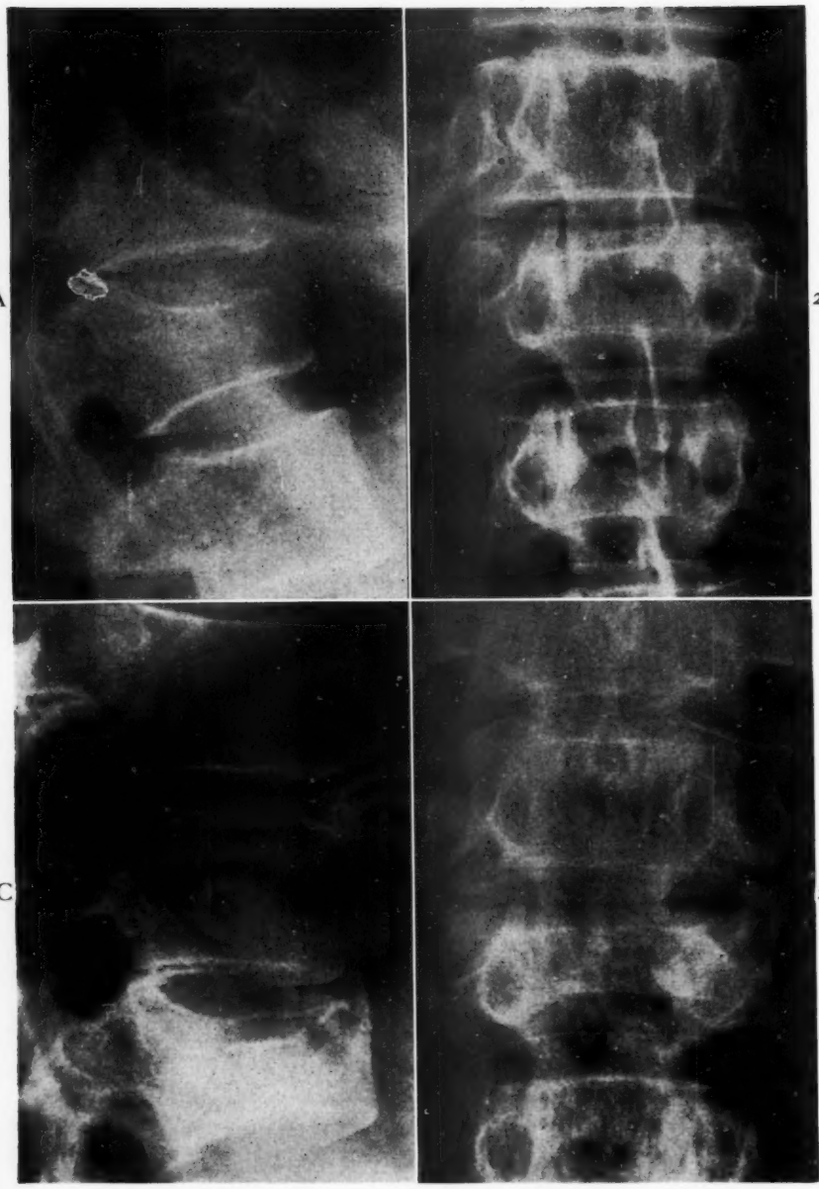
Thirty-six patients with spinal fusion for compression fracture of a vertebral body have been followed up for more than five years, with an average follow up of eleven years. The fusion operation was done within two months in fifteen cases and later in twenty-one cases. With early fusion the symptomatic and functional results were excellent or good in 92 per cent. These patients had no significant pain, weakness or disability and were able to lead normal lives including heavy work. The range of motion beyond the fusion was not restricted. Roentgenograms revealed complete healing of the fracture, as well as solid fusion. The results when fusion was done later were good or excellent in all of the thoracic cases and 83 per cent of the lumbar cases. Only one patient was unable to return to his former occupation. The convalescent period for these later cases was a little longer than when the operation was performed early. The results in the group with spinal fusion were better than the group without fusion and the convalescent period was shorter.

Convalescence after fracture of the spine is likely to be slower in the presence of osteoarthritis with lipping or spurs, and the result less satisfactory. Convalescence is slower after the age of forty, and the likelihood of returning to heavy labor lessens with age.

CONCLUSIONS

1. The differential diagnosis of compression fracture of the spine is important, especially when there may be concomitant disease or a malignant tumor.

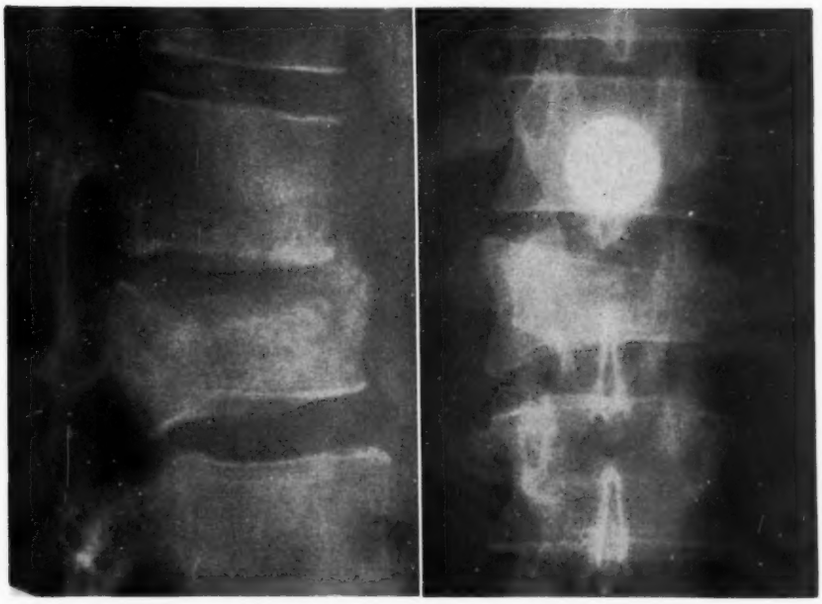
2. It is difficult by conventional methods to



23A 23B

23C 23D

FIG. 23. A and B, September 6, 1951. Lateral and anteroposterior views. Moderate wedging and compression of the superior plate of the body of L1, with moderate kyphosis. The superior lateral corner is displaced as a free fragment. The body is expanded laterally. Note the triangular bony mass above the anterior-superior edge of T12, an accessory ossification center, which should not be confused with a fracture. C and D, December 4, 1951. Lateral and anteroposterior views. The same fracture three months later. Little or no reduction was obtained by hyperextension in a reverse Gatch bed. A spinal fusion, Hibbs type, was done six days after injury (T12-L2) and bedrest was continued for six weeks with a Taylor brace. The patient wore a brace when ambulant for an additional eight weeks. The symptomatic and physical results were excellent despite the persistent deformity. The patient returned to heavy work six months after injury without pain or handicap. Note the solid fusion.



24A 24B

FIG. 24. A and B, June, 1951. Lateral and anteroposterior views. Moderate compression and moderate wedging to one side, with comminution laterally and through the center of the body and the inferior plate of L1. The disk at T12-L1 is ruptured into the body of L1. There is moderate posterior expansion of the body into the spinal canal. However, there were no neurologic signs. The articular processes and laminas escaped fracture. There is a moderate kyphos. There were also severe comminuted fractures of the calcanei. Hyperextension resulted in little or no correction of deformity. An early spinal fusion, Hibbs type, of T12-L2 was done, followed by recumbency for eight weeks in a Taylor brace. The brace was worn altogether for three and a half months. The clinical result was very good with a four-year follow-up. The patient returned to his previous moderately active work.

obtain true correction of the wedge deformity characteristic of traumatic compression fracture of the spine, and more difficult to maintain it.

3. Compression fractures of vertebral bodies always heal, and the results are usually good with or without correction if there is no significant joint damage or disalignment of the spine.

4. Significant joint damage, prolonged immobilization or inactivity or osteoarthritis lead to prolonged convalescense and poorer results after vertebral fracture.

5. Severe compression or comminution of a vertebral body, or fracture-dislocation may in time be followed by a good result if spontaneous anterior bony ankylosis occurs and if postural alignment of the spine is not seriously disturbed.

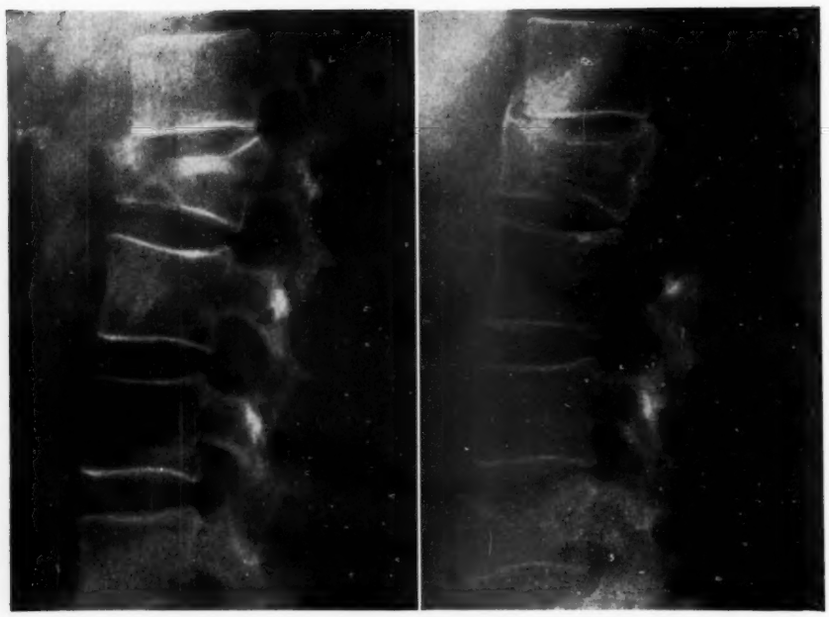
6. Fracture of a posterior vertebral process is not uncommon, and is most likely to result in persistent pain and disability.

7. Spinal fusion, when properly performed, is accompanied by a high percentage of good results, especially if used early in the treatment of vertebral fracture.

8. Spinal fusion is indicated especially for young people who wish to lead vigorous lives and for older people who must do heavy work. It is indicated for moderate or severe compression fracture, with or without correction, especially if there is significant joint damage, particularly in the lumbar region. The convalescence will be shorter in such cases, and the result better than with non-operative treatment.

9. Spinal fusion is indicated for most comminuted vertebral body fractures, for fractures of the posterior arch, for some fracture-dislocations, and sometimes combined with a neurosurgical procedure.

10. Early spinal fusion gives better results than late fusion. Spinal fusion gives better results than other forms of treatment for these types of vertebral fractures, and results in a saving of time and money. It permits an earlier



25A 25B

FIG. 25. A, January, 1938. Moderate compression and wedging of the body of L1 with comminution of the superior plate, a vertical fracture through the body, and anterior and posterior expansion. The disk T12-L1 is thinned and ruptured into the body. There is a moderate kyphosis. No neurologic signs were noted. Pain and disability would be expected after the usual treatments. Moderate correction was obtained with reverse Gatch hyperextension. A spinal fusion, Hibbs type, was done five days after injury. The patient wore a Taylor brace and hyperextension for eight weeks in bed and then eight weeks ambulant. He returned to heavy work six months after injury. B, December, 1941, four years after injury. Correction has been maintained and the patient has continued heavy work without pain or disability. Fusion is solid and mature and there is bony bridging anteriorly. The patient returned because of another fall with injury to the back. There is now a compression fracture of the body of L4, but no fracture of L1 or of the fusion mass which withstood the fall without harm.

return to heavy work, and allows some patients to do heavy work which they could not otherwise do.

11. Postural disalignment of the spine or increased lumbar lordosis after fracture is likely to result in backache and disability, especially in the lumbosacral region, more so if there is already a pre-existing unstable lumbosacral joint. Lumbosacral fusion is often indicated in such cases.

12. Immobilization and inactivity with any form of treatment for vertebral fracture should be reduced to a minimum, whereas exercises should be begun early and practised faithfully.

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Skin Sloughs Associated with Levophed

PATHOGENESIS, PREVENTION AND TREATMENT

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LEVARTERENOL (levophed®) is a powerful vasopressor which functions by causing generalized vasoconstriction without any change or a slight decrease of cardiac output. It has been proved to be of value in cases of shock due to various causes including coronary thrombosis, hemorrhage, trauma, central depression, septicemia and the like. When administered as a slow intravenous drip, levarterenol is a most efficacious means of combating hypotension. The most common detrimental effect accompanying the use of this drug has been necrosis of the overlying skin when the solution has accidentally become extravasated. Skin necrosis has also been reported at sites distant from the point of infusion along the course of the vein in use even though no extravasation has occurred. The latter has been seen only in lower limbs with already impaired arterial supply.[1–5]

A suitable means of combating or preventing the damage due to extravasation of levarterenol would be most valuable. In an attempt to prevent gangrene in a patient who had sustained an extensive, prolonged infiltration of levarterenol, the authors locally infiltrated the area with phentolamine (regitine®).[6] The possible value of this drug was suggested because it is an adrenolytic compound and physiologic antagonist to epinephrine and norepinephrine (levarterenol). Its ability to counteract circulating nor-adrenalin has made it a valuable tool in diagnosing pheochromocytomas.

The results in this one case seemed so satisfactory that experiments were set up to check the validity of the initial observation. During the period the trials were being carried out, infiltration of levarterenol occurred in three additional cases. The results of the animal experiments and the treatment of the human cases are the subject of this report.

EXPERIMENTAL INVESTIGATIONS

Since it was impossible to run adequate controls on experiments of this type in human beings, it was decided to carry out protection studies on experimental animals. Twenty domestic rabbits were chosen for use. The first part of the study was devoted to finding a means of administration which could cause necrosis in 100 per cent of the subjects. The consistent production of skin necrosis by a single injection of levarterenol proved impossible. Even though an undiluted solution of levophed containing 0.1 per cent levarterenol was administered subcutaneously in one dose, no visible damage occurred. After exhaustive studies of single dose administration of levarterenol, it became apparent that this method of administering the drug was benign. It was found, however, that *continuous subcutaneous administration* would produce necrosis. No appreciable results were obtained until the period of administration was prolonged to over one hour. The extent of the damage produced seemed to be a function of the time of exposure

rather than of the total amount of levarterenol introduced or of its concentration.

These results were checked on ten more animals. Domestic rabbits weighing 2 kg. were used; they were restrained in the supine position with their abdomens shaved, and 4 mg. of levarterenol in 250 cc. of 5 per cent glucose in water were administered by subcutaneous clysis. The period of administration was 130 to 170 minutes.

Three rabbits, Nos. 10, 11 and 12, were given 250 cc. of 5 per cent glucose in water over a similar period to serve as controls.

Nine more rabbits were then given the standard infusion of glucose and levarterenol in water. However, within one-half hour of the termination of the infusion, each of these animals received 5 mg. of phentolamine (regitine) in 15 cc. of normal saline with 125 turbidity-reducing units of hyaluronidase added to aid diffusion. This mixture was carefully injected subcutaneously with a 4-inch No. 22 gauge needle into the entire area previously infiltrated by the levarterenol. This was identified by the pallor and frigor which clearly demarcated it from surrounding normal tissues. (Fig. 1.)

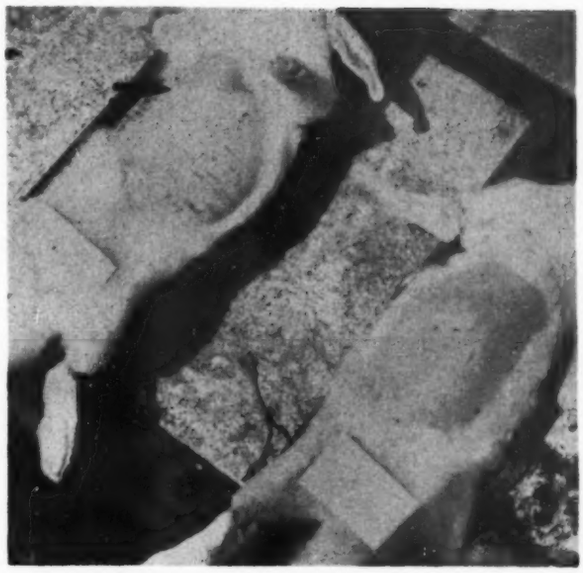

FIG. 1. Two rabbits immediately after termination of 250 cc. subcutaneous infusions of 4 mg. of levarterenol in 5 per cent glucose in water (upper left) and plain 5 per cent glucose in water (lower right). Note intense blanching in rabbit on left. (Arrow indicates line of demarcation.)

RESULTS

Untreated Animals (Receiving Levarterenol in 5 Per cent Glucose). The gross changes observed in the infiltrated skin may be outlined as follows. Immediately upon termination of the infusion, the area was blanched, pure white, boggy with unabsorbed fluid and clearly demarcated from the surrounding normally pink skin. (Fig. 1.)

Eighteen hours after the termination of the infusion, the skin of the affected area was covered with bluish brown ecchymoses, giving an over-all mottled appearance. The skin was an unnatural glistening pearl-white between the ecchymoses. Edema could no longer be seen and no breaks in the continuity of the epithelium were visible. Skin turgor was reduced, but when pinched, the skin slowly assumed natural contours.

In twenty-four hours the ecchymoses had coalesced in some locations into bluish brown lesions 1 by 2 cm. in area. There was a complete loss of skin turgor and the skin felt unusually freely movable. There was no edema, nor were any breaks in the skin visible.

At forty hours all the aforementioned changes were more marked; the ecchymoses had involved almost all the affected skin. Pitting edema developed in the area and several large blebs (3 by 6 cm.) made their appearance. One blister was evacuated and was found to contain clear fluid resembling serum.

At sixty-nine hours the skin was lax, wrinkled and covered with blue-brown ecchymoses; the non-ecchymotic areas were pasty white. All turgor had disappeared and most of the blisters seemed to have resorbed at least partially. Overt breaks and signs of infection were becoming apparent. (Fig. 2A.)

At eighty-seven hours the involved areas were frankly gangrenous; pus could be observed exuding from the edges of a hard matted mass of dead skin and hair which was all that remained of the original infiltrated area. When gangrene appeared, the animals were sacrificed.

Biopsies. Full-thickness skin biopsies were obtained from the affected area at intervals of twenty-four hours for as long as seventy-two hours. In both animals from which these biopsies were obtained, the changes were similar. It is interesting to note that the changes observed in the small blood vessels of the area were not any more advanced than the pathologic alterations of the dermis and sub-

FIG. 2A. Definite necrosis sixty-nine hours after levarterenol infusion.

FIG. 2B. Prevention of necrosis in rabbit receiving regitine after levarterenol infusion.

cutaneous tissue. No thrombosis or angiitis could be discerned.

The major process could be described as a gradual coagulation necrosis equally affecting all components of the tissue, so that within seventy-two hours little or no living tissue can be discerned. The pathologic changes may be summarized as follows:

In twenty-four hours the only changes noted were extracellular edema and scattered extravascular erythrocytes. In forty-eight hours there was necrosis of the surface epithelium and hair follicles with hyalinization; extravasated erythrocytes were still present and collagen fibers were swollen and frayed. At seventy-two hours all these changes were more pronounced and the nuclei of hair follicle cells had disappeared. These changes are illustrated in Figures 5 to 8.

Controls (Animals Only Given 250 cc. of 5 Per cent Glucose). The three rabbits that received clyses of 250 cc. of glucose in water without levarterenol showed only a transient edema. There was no necrosis of tissue and biopsy specimens were not obtained.

Treated Animals (Levarterenol Clyses Followed by Local Infiltration of Regitine). In nine rabbits following the levarterenol clyses, 5 mg. of phentolamine regitine) in 15 cc. of saline (with 125 units of hyaluronidase) were injected into affected areas. These areas could be clearly demarcated from the normal tissue by the pallor and frigor. Within twenty minutes of the administration of this solution, patches of hyperemia could be seen in the blanched area. (Fig. 3.) One hour later the skin of the entire abdominal wall was warm and hyperemic. (Fig. 4.) After twelve hours no trace of edema could be found and the area was indistinguishable from surrounding normal skin. Observation of these animals for a period of one week failed to reveal necrotic changes in the injected area. All survived without evidence of slough after two weeks of observation.

These laboratory experiments conclusively demonstrated that levarterenol infiltration into the subcutaneous tissue can produce necrotic changes in the skin and that the necrosis can be prevented by the injection of regitine into

FIG. 3. Appearance of skin twenty minutes after infiltration of regitine.

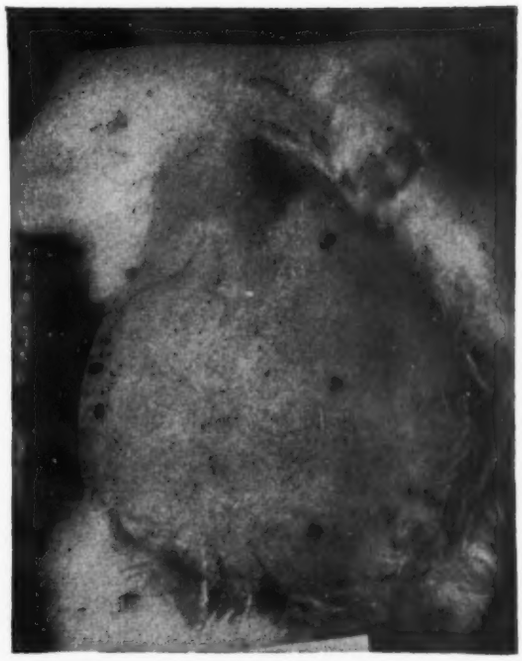

FIG. 4. One hour after infiltration of regitine. Area of demarcation less sharply delineated as compared to Figure 3.

the affected area. That this procedure can be applied effectively in clinical practice can be noted in the following case reports.

CASE REPORTS

CASE 1. C. N., a forty year old nurse, underwent an uneventful cholecystectomy, but immediately postoperatively she became cyanotic, pink frothy sputum was noted in the mouth, and the pulse rate rose to 150 per minute. Both lungs showed moist rales throughout; the blood pressure was 130/70 mm. Hg. The electrocardiogram showed sinus tachycardia with low T waves in all precordial leads, but no evidence of myocardial infarction was noted. The response to therapy was very poor. The blood pressure fell to 70/55 mm. Hg.; the rales and tachycardia persisted. An infusion of levarterenol, 4 mg. in 1,000 cc. of 5 per cent glucose and water, was started in a vein in the left forearm. A satisfactory blood pressure response could only be obtained if the solution ran at a rate of sixty or more drops per minute. Because of the obvious danger of administering large amounts of intravenous fluid in the presence of left ventricular failure, a more concentrated solution—one containing 16 mg./1,000 cc.—was substituted. This produced satisfactory blood pressure levels at a rate of approximately twelve drops per minute. The pulmonary edema gradually subsided, but the blood pressure could not be maintained without continuous intravenous levarterenol. After the infusion had been running for approximately twenty hours, it was noted that the levarterenol solution had infiltrated the skin of the forearm and antecubital fossa. As far as could be ascertained, this had continued for forty-five to sixty minutes before it was noticed.

The area of skin involved measured 7½ by 19 cm. The skin was blanched, cold, indurated and was clearly demarcated from the surrounding skin. It was believed that this area would probably become necrotic. Accordingly, a solution containing 5 mg. of regitine and 125 turbidity-reducing units of hyaluronidase in 10 cc. of normal saline was injected subcutaneously with a long No. 22 gauge needle. Half of the involved area was thus injected; the remainder was left as a control. Within three to four minutes of the injection, the area treated with regitine became warm, pink and blanched on pressure. The remaining half of the area, not injected, continued to be white, cold and indurated. This response appeared so beneficial that a similar solution was injected into the remainder of the involved area with the same results.

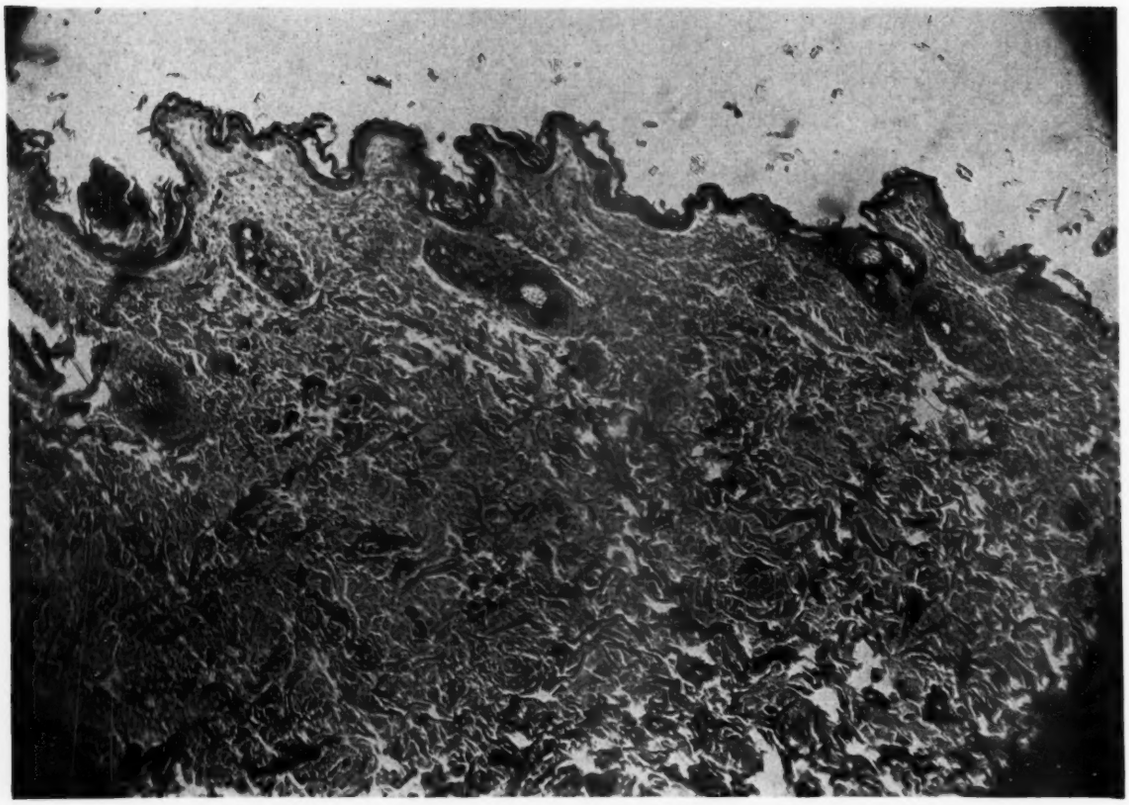

FIG. 5. Normal rabbit skin obtained by biopsy immediately before levarterenol infusion.

Despite the fact that 10 mg. of regitine had been injected, there was no hypotensive effect and it was not necessary to increase the rate of flow of the levarterenol infusion which had been reinserted into another vein.

On the second day the involved skin was hyperemic and was noticeably warmer than the rest of the body; there was no vesiculation, scaling or other trophic change. On the third day, when it was finally possible to discontinue the levarterenol infusion, the treated area was still slightly warmer than the rest of the body. Subsequently, the involved area became indistinguishable from the surrounding skin. The patient was discharged on the twentieth postoperative day in good condition. Follow-up has revealed no deterioration of the treated area.

CASE II. G. W., a sixty-four year old white man with malignant hypertension, had inadvertently administered to himself an overdose of pentolinium tartrate (ansolysen®). His blood pressure was unobtainable even in the supine position, and he began to experience substernal distress.

An infusion containing 8 mg. of levarterenol base in 1,000 cc. of 5 per cent glucose in water was started in a vein of the dorsum of the left hand. The blood pressure soon rose to satisfactory levels. Shortly thereafter the needle became dislodged from the vein and the solution flowed subcutaneously for approximately thirty minutes before being noticed. The hand was puffy, pallid and extremely painful. Regitine, 5 mg. in 10 cc. of normal saline with 125 turbidity-reducing units of hyaluronidase, was infiltrated throughout the area.

Within five minutes normal color returned and the pain and tenderness were greatly alleviated. Within one hour the area could hardly be distinguished from normal skin. The patient was discharged one week later with no evidence of damage to the skin.

CASE III. F. K., a sixty-two year old white man, was admitted to the Long Island College Hospital with peritonitis secondary to a ruptured appendix. He was placed on antibiotics and supportive therapy, but his condition steadily deteriorated. He eventually became hypotensive and an infusion of levarterenol was

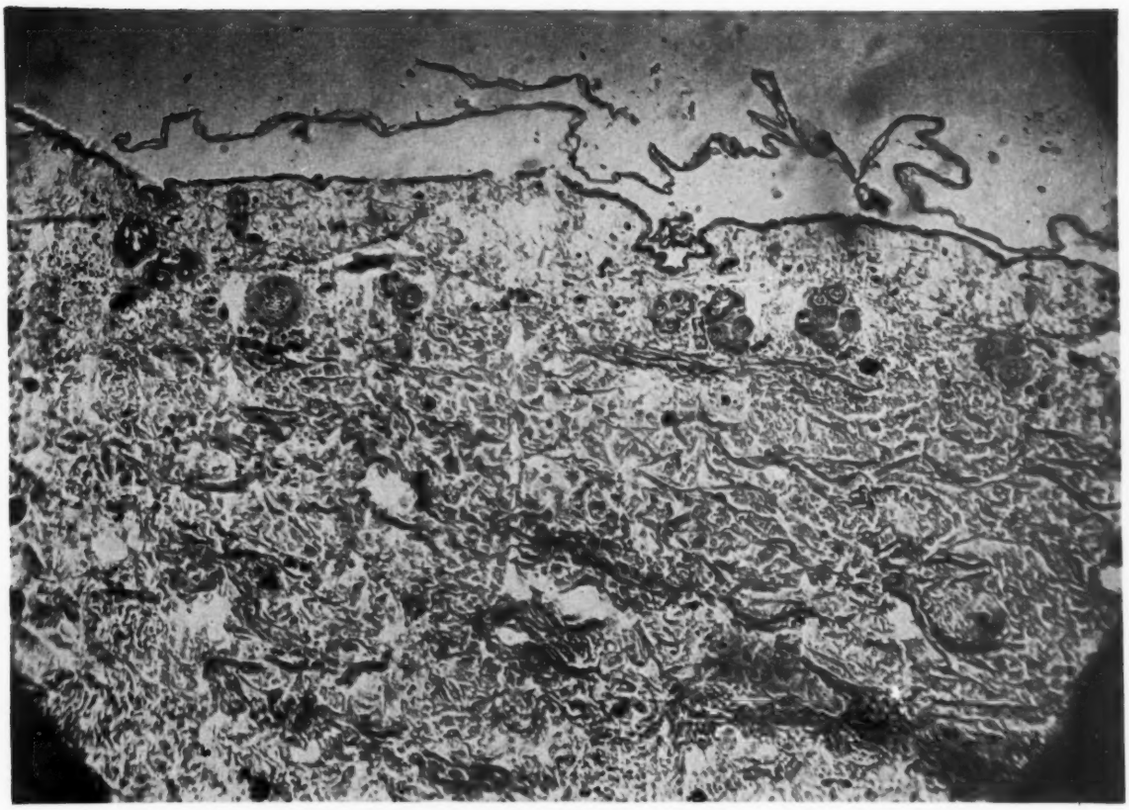

FIG. 6. Rabbit skin twenty-four hours after levarterenol infusion. Swelling of collagen fibers evident.

started in a vein on the lateral aspect of the left wrist. The blood pressure rose immediately to satisfactory levels, but in a short time the needle was dislodged. The infusion continued to run rapidly and thus, the extravasation was not noticed until a large area on the wrist became involved. The area was cold, blanched and tender. The estimated time of infiltration was thirty minutes.

The infusion was discontinued and inserted at another site. Meanwhile, the infiltrated area was treated with regitine, 5 mg. in 15 cc. of normal saline with 125 turbidity-reducing units of hyaluronidase. The area began to assume normal color within five minutes and within twenty minutes was hyperemic. No drop in blood pressure or increased need for levarterenol could be noted.

The patient died thirty-six hours later from his primary disease; up to the time of death no changes were noted at the site of extravasation.

CASE IV. C. S., a fifty-four year old retired merchant with a long history of chronic pulmonary emphysema and fibrosis with cor pulmonale, entered the Long Island College Hospital with a history of twelve hours of weakness, coldness and diaphoresis. His blood pressure was 100/60, pulse 110 and regular, and his respiratory rate was 30. His lungs showed rhonchi and occasional moist rales at the right base. The remainder of the physical examination was non-contributory.

Six hours after admission acute pulmonary edema and profound shock suddenly developed. The lungs were full of moist rales to the apices and no pulse or blood pressure readings were obtainable. Oxygen, supplemental digitalis and mercurial diuretics were administered and an intravenous drip containing 8 mg. of levarterenol base in 500 cc. of 5 per cent glucose in water was started in a vein on the lateral aspect of the right wrist. It was found that lower concentrations of levarterenol would not sustain the blood pressure. Within a few minutes the patient's disoriented struggling dislodged the needle and the solution infiltrated the site, producing a rectangular area of frigor, pallor and induration measuring 3 by 8 cm. The intravenous injection was reinstituted subsequently in the other wrist, with the same results. The infusion was then administered

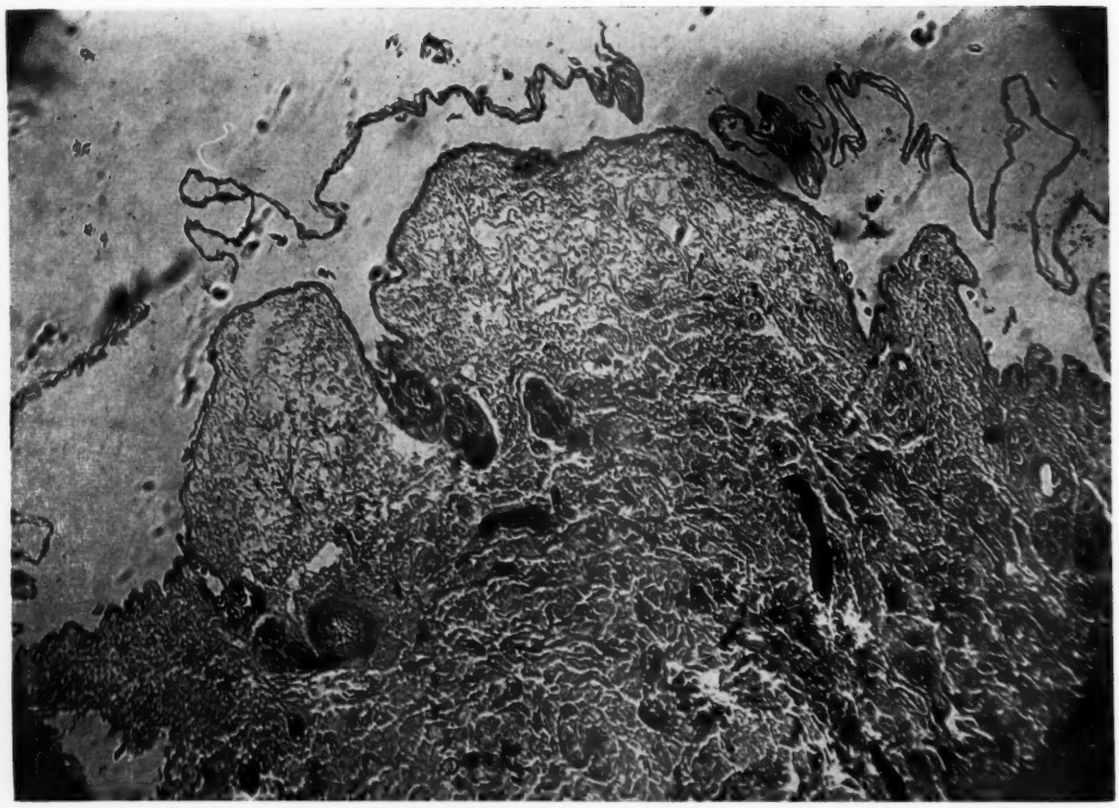

FIG. 7. Rabbit skin forty-eight hours after levarterenol infusion. Fraying of collagen fibers and necrosis of hair follicles.

via a catheter introduced into the exposed lessor saphenous vein at the ankle.

Meanwhile, the area on the right wrist was treated with phentolamine and hyaluronidase. It soon lost its tenderness and pallor, and within three hours was indistinguishable from normal skin. At this time the patient was complaining bitterly of pain and tenderness in his left wrist. The wrist was intensely pale, swollen and cold, and small ecchymoses were seen. The phentolamine treatment was repeated here. All signs of vasospasm disappeared within one hour and the pain was relieved immediately.

After the highly concentrated levarterenol infusion had been running in the ankle vein for two hours, the patient began to flex and extend his right leg and complained of burning pain in the right calf. It was noted that a diamond-shaped area of skin 12 by 15 cm. in its greatest dimensions on the medial aspect of the right calf and knee was intensely pale and cold. There was no edema, the area did not blanch on pressure and was tender to palpation. The end of the polyethylene catheter could be felt at the distal end of the blanched area. This area was also infiltrated with phentolamine; the tenderness and pain disappeared in minutes and within two hours the color was blending with surrounding normal skin. Despite the fact that the infusion was allowed to run in the same vein for six hours after phentolamine was administered, no further vasospasm could be detected in the area treated.

Six hours later it was possible to discontinue the levarterenol infusion. The only discernible alteration was a linear patch of ecchymosis at the proximal end of the diamond-shaped area, and one round patch 2 cm. in diameter in the center of the treated area. These remained warm but seemed to resorb slowly. It was noted that both these areas had probably been missed when infiltration with phentolamine was performed. The round area was midway between two needle marks and the linear ecchymosis was beyond the area marked as blanched and cold; its shape suggested that it was the periphery of the affected area and had been inadequately reached by the phentolamine.

None of the injections of phentolamine produced any alteration in blood pressure or in-

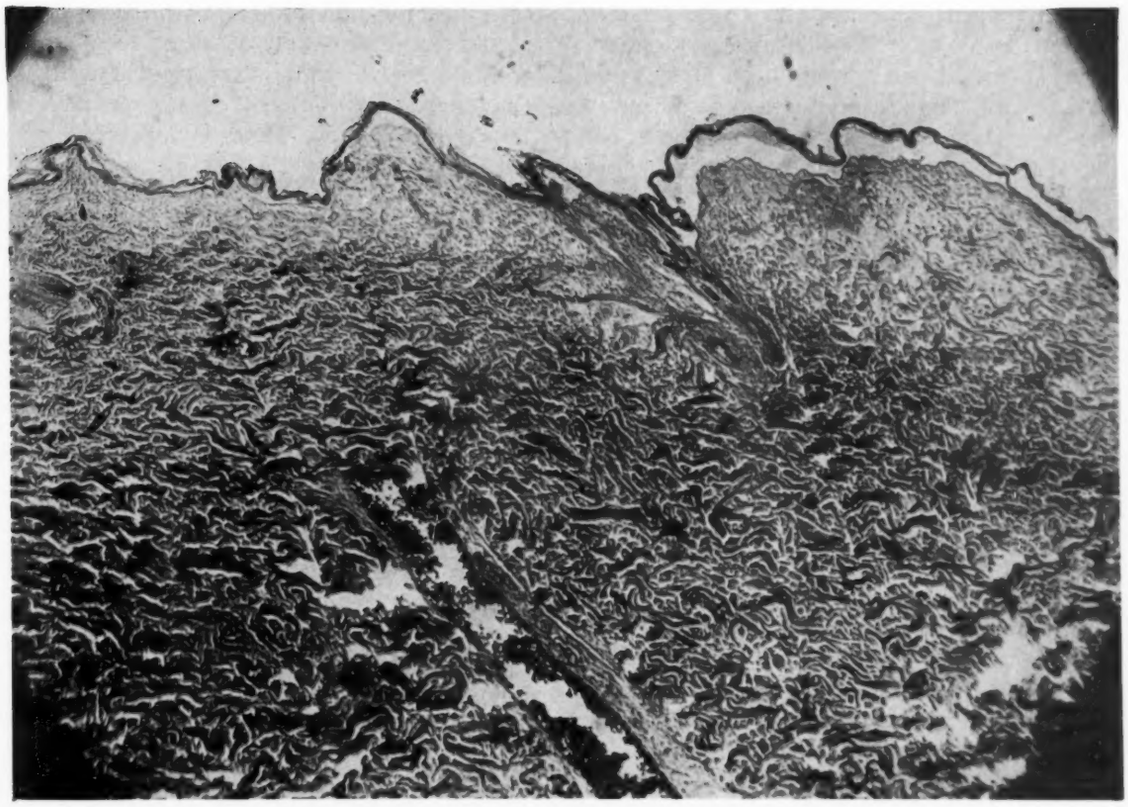

FIG. 8. Rabbit skin seventy-two hours after levarterenol infusion. Further necrosis and hyalinization in all layers. Blood vessels show thickened basement membrane.

crease in levarterenol requirement. Subsequently, a pulmonary infarction was noted and the patient died five days later. Observation of the involved area disclosed only the persistence of the two sites of ecchymosis, which were resorbing well at the time of death.

COMMENTS

The occurrence of necrosis in patients receiving intravenous levarterenol is infrequent, but the widespread use of this drug will undoubtedly increase its incidence. The authors have observed about twelve cases in which gangrene developed and several more in which skin changes were present although necrosis did not supervene. The lesions produced in these cases, even though they usually resolve, are exquisitely tender and painful and often require opiates for relief of the pain. Occasionally skin grafting may be necessary.

Most cases of slough have occurred in the lower extremities, although the authors have also observed necrosis on the dorsum of the hand and antecubital fossa. It is postulated that in the lower extremities necrosis is liable to develop because the legs are so frequently the site of arterial and venous disturbances which reduce total blood flow and also slow the rate at which levarterenol flows from the area. Patients receiving levarterenol are usually in shock and suffer from the impaired peripheral circulation associated with this condition. Thus, local circulatory insufficiency is even more prone to develop.

It has been previously recommended that leg veins be avoided as sites for infusion of levarterenol.[6–8] This would seem advisable when possible, especially in older patients with arterial impairment. Cases have been reported (as noted previously) in which deep necrosis occurred along the course of the vein in use distant from the site of infusion, even though no extravasation could be demonstrated. This has been explained as a result of changes in vessel permeability due to intense spasm of the vasa vasorum of the involved vein, which allows seepage into surrounding tissues.

The authors have shown that continued infusion of levarterenol is necessary to produce gangrene. This period during which the drug is

presented to the tissue appears to be a more important factor than total dosage or concentration. It would seem then that meticulous observation of the site of infusion and course of the vein would probably detect the early pallor, frigor and induration in time to avert irreversible changes.

If any of these signs of local vasospasm and ischemia due to levarterenol are observed, it would seem wise to change the site of infusion. As soon as possible, phentolamine should be injected subcutaneously throughout the affected area. To ensure adequate penetration, 5 mg. of phentolamine may be dissolved in 15 to 20 cc. of normal saline and 125 turbidity-reducing units of hyaluronidase added. In Case IV it was possible to continue the levarterenol infusion after the blanched area had been treated with phentolamine without changing the site of infusion.

Phentolamine has been shown to produce an initial vasodilatation lasting up to ten minutes, followed by adrenergic blockade for several hours.[9] During this period it would appear that the blood vessels of the skin would be insensitive to the influence of extravasated levarterenol. Thus, the possibility exists of continuing infusions through catheters after protection with phentolamine when it is definitely known that there is no gross extravasation.

In all patients receiving levarterenol who were treated with locally injected phentolamine, the blood pressure was unaffected. Thus no change in the rate of levarterenol administration was necessary.

From our experience with both humans and animals it appears that phentolamine (regitine), when administered shortly after the occurrence of nor-epinephrine extravasation, will completely prevent irreversible damage. It is recommended, therefore, that this drug be available when levarterenol is being used. Careful choice of the site of infusion, constant vigilance for the first signs of local ischemia and immediate administration of phentolamine when needed will prevent most cases of necrosis associated with the use of levarterenol.

SUMMARY

1. An experimental method of producing skin necrosis by subcutaneous infusion of levarterenol is presented. It is the authors' opinion that length of time of administration is the main factor in producing necrosis, rather than concentration or amount infiltrated.

2. A method of preventing such slough by administering regitine with hyaluronidase locally into affected areas is presented.

3. The clinical application of this method in four patients is presented.

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Sialography

A NON-IRRITATING MEDIUM

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IN reporting the results of experimental work with non-volatile substances and their effect upon the salivary glands during sialography,[1] the author found that the use of the glyceryl ester of poppyseed oil produced a very marked foreign body reaction within the gland substance. The gland itself was considerably enlarged with moderate periductal round cell infiltration and extensive fibrosis. Many giant cell granulomas were seen on section with focal areas of necrosis. Many of the ducts were completely obliterated and the ductal epithelium revealed a marked proliferation. It was obvious that this substance was not the most ideal vehicle for sialography. (Figs. 1A and B.)

A very interesting substance, ethiodal,* was brought to the attention of the author by Dr. Alfred Halpern, Medical Director of E. Fougera and Company. Ethiodal is an ethyl ester of the iodinated fatty acids of poppyseed oil and has a greatly reduced viscosity because of a simpler molecular structure. The increased fluidity is an asset when injecting such media into a closed circuit of a very fine trabecular structure, although the fluidity of the glyceryl ester can be increased by simply placing the solution in a pan of warm water. To continue with the experimental work to find a medium with little or no foreign body reaction, the ethyl ester of the iodinated fatty acids of poppyseed oil was injected into the ducts of the submaxillary glands of three dogs and the glands were removed at intervals of two, four and eight weeks. Sections were made of these glands. Gross examination revealed no evidence of any foreign body reaction. There was no round cell infiltration, no areas of necrosis, either interstitial or focal areas, no giant cell granulomas, and the ducts and their epithelium

* Manufactured by E. Fougera and Company, New York, New York.

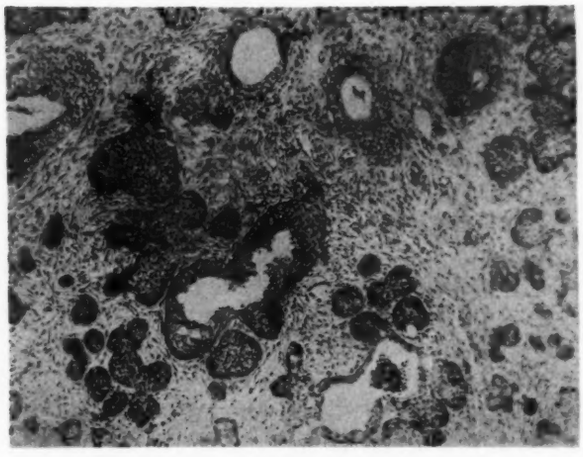

FIG. 1A. Glyceryl ester of poppyseed oil injection; severe foreign body reaction with many granulomas. Considerable fibrosis and focal areas of necrosis (original magnification × 85).

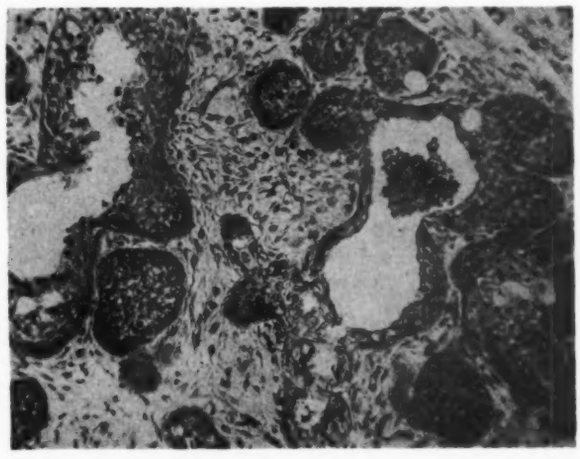

FIG. 1B. Glyceryl ester of poppyseed oil injection; severe foreign body reaction with many granulomas. Considerable fibrosis and focal areas of necrosis (original magnification × 170).

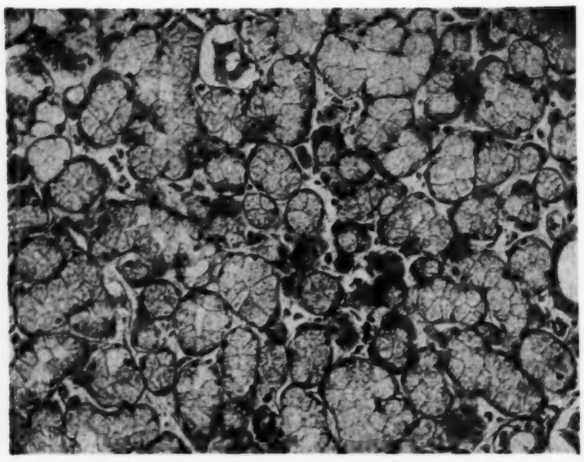

FIG. 2. Ethyl ester of poppyseed oil (ethiodal). Gland removed two weeks after injection; no evidence of any foreign body reaction (original magnification × 125).

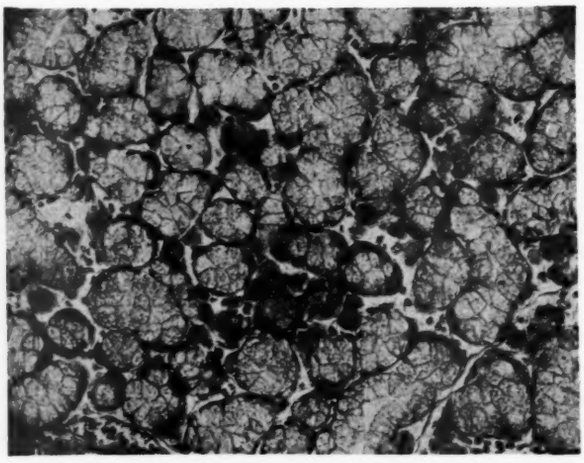

FIG. 3. Ethyl ester of poppyseed oil. Four weeks after injection parenchymatous cells reveal normal secretory activity without irritation or interstitial involvement (original magnification × 125).

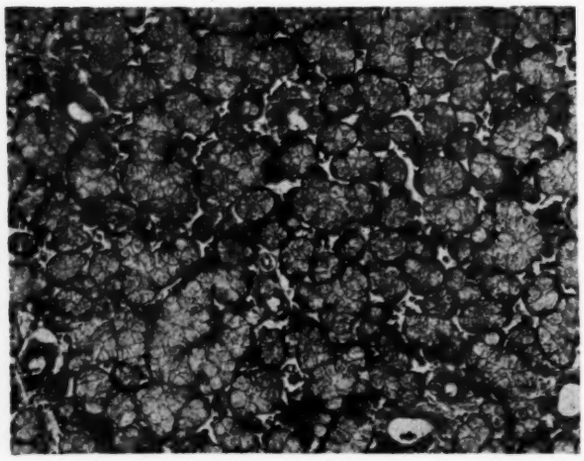

FIG. 4. Same drug, eight weeks after injection; ducts and ductal epithelium normal. No anatomic or physiological changes present.

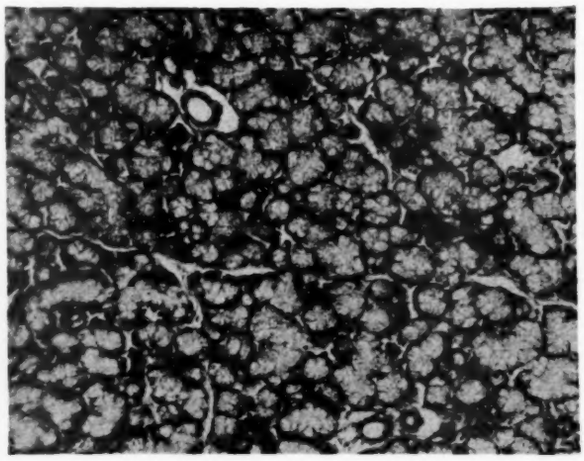

FIG. 5. Diiodo pyridone acetate of diethanolamine in polyvidone; glands removed in two weeks. No evidence of any disturbance in function, parenchymatous or ductal structures. Glands apparently returned to normal very rapidly and remained so (original magnification × 125).

revealed no changes. (Figs. 2 to 4.) The simple change in molecular structure created a non-irritating and more freely flowing substance. It is evident also that a comparatively simple revision of the molecular structure of a chemical substance can and does change the physiologic effect upon living tissues.

The diiodo pyridone acetate of diethanolamine in polyvidone, which is a plasma expander, was also injected into the lumen of the (submaxillary) submandibular salivary glands of a similar number of dogs and the glands removed at two, four and six weeks. Similarly there was no evidence revealed of a foreign body reaction either in the parenchyma or interstitial tissues, or ductal epithelium. (Figs. 5 to 7.)

The viscosity of both these media are comparable, and to test them further for their value they were injected into the salivary glands of patients. The ethyl ester of the iodinated fatty acids of poppyseed oil proved to be far more satisfactory from a diagnostic standpoint, because it is much more radiopaque than diiodo pyridone acetate of diethanolamine in polyvidone. This may be due to the fact that polyvidone is absorbed very rapidly.

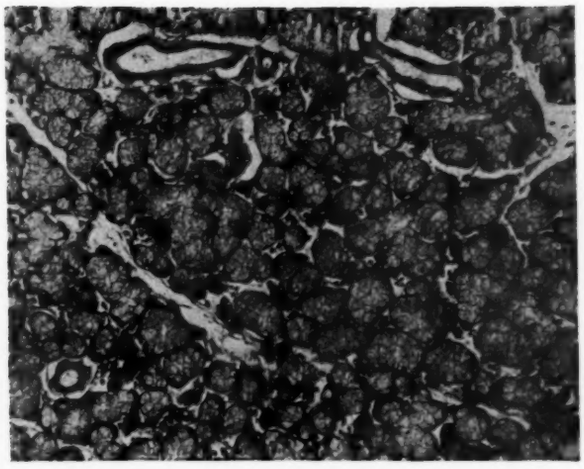

FIG. 6. Diiodo pyridone acetate of diethanolamine in polyvidone; glands removed in four weeks. No evidence of any disturbance in function, parenchymatous or ductal structures. Glands apparently returned to normal very rapidly and remained so (original magnification × 125).

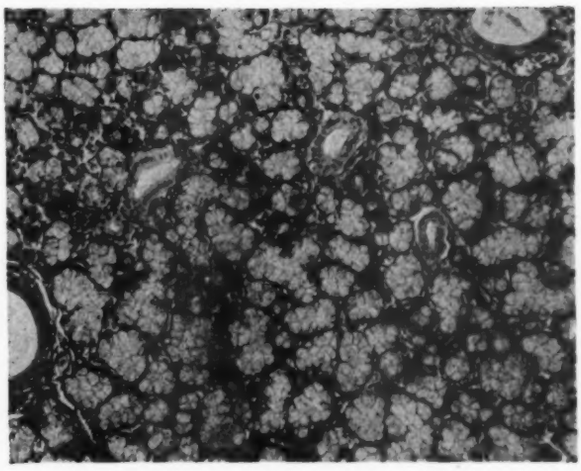

FIG. 7. Diiodo pyridone acetate of diethanolamine in polyvidone; glands removed in six weeks. No evidence of any disturbance in function, parenchymatous or ductal structures. Glands apparently returned to normal very rapidly and remained so (original magnification × 125).

SUMMARY

From the foregoing experiments it is obvious that molecular readjustments in a chemical can, and do, change the physiopathologic effect on salivary glands. Whereas the glyceryl ester of poppyseed oil was found to be very irritating with the production of a marked foreign body reaction within the gland substance, the ethyl esters of the fatty acids of the same poppyseed oil produced no evidence of irritation or foreign body reaction.

CONCLUSION

The ethyl esters of the fatty acids of poppyseed oil offer an excellent medium for contrast studies of salivary glands.

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Consideration of the Use of Dermal Grafts in the Repair of Hernia

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SURGEONS are still searching for an operative technic of hernia repair with a higher rate of cure than that given by the older classic methods.

When muscular weakness or a poor quality of muscular tissue exists at the inguinal region it is generally considered that the simple removal of the hernial sac high at its neck is insufficient to secure a good permanent result. Following failures from Bassini's method, many other operations have been practiced which, for the most part, have one common object, namely, to strengthen the floor of the inguinal canal and also the internal inguinal ring.

This has been affected on the one hand by the introduction of foreign substances such as flossilk[1] and filigree (McGavin), and on the other hand by the use of autogenic tissues such as sac (McEwan, 1886), rectus sheath and muscle,[2,3] cremaster[4] and fascia lata.[5]

It is notable that in cases in which autogenous tissue was used, this tissue, although taken from the patient's own body, was devascularized completely in the case of free transplants and almost completely in the case of hinged flabs so that the tissue had little chance of survival. It must be admitted that the reaction to the introduction of dead autogenous material is likely to be less than to foreign substances, yet both predispose to infection if organisms gain access at the time of operation.

The method described by Mair[6] seeks to strengthen the posterior wall of the inguinal canal by the introduction of a "free" skin flap. This, almost of necessity, introduces skin organisms but, as Mair showed, sepsis occurred only occasionally, which I believe is due to the rapid revascularization of the graft. Mair also showed that the epithelium of the graft disintegrates rapidly, leaving a firm plaque of fibrous tissue; the latter fact also is advocated by Ali[7] who uses a cutis strip in Gallie type repair of large inguinal hernias.

Intrigued by Mair's publication in 1945, I have since made use of this particular repair in cases of large or recurrent inguinal hernias, in hernia repair on patients with pronounced muscular weakness, as well as in cases of incisional hernia.

The method employed closely follows that described by Mair. The skin is prepared by cleaning with phisoderm twenty-four hours before operation and a sterile dressing is applied. An ellipse of skin, about 3½ inches in size, is excised within the usual landmarks, opening the inguinal region in the usual way. The excised skin flap is freed from all subcuticular fatty tissue and placed in normal saline at body temperature. The cremaster is slit in the usual way, the sac is dissected high to its neck, revised after opening and resected with the stump transfixed under the internal oblique muscle. The graft then is slit longitudinally for two-thirds of its length at its proximal end. While the distal (lower) angle of the graft is fixed by a suture to the pubic spine, the lateral edge is fixed by interrupted cotton sutures to the shelving edge of Poupart's ligament. The cord, after closure of its slit, is led through the split in the graft, and the medial edge of the graft is fixed by means of interrupted cotton sutures to the free margin of the internal oblique muscle and the conjoint tendon under some tension. The slit in the graft also is closed with interrupted sutures, thus forming a new inner ring as well as a new floor of the inguinal canal.

The method of a free skin implant also can be used successfully in repair of incisional hernias. Here, in a similar way, the free flap is implanted into the defect of the abdominal wall, usually using the excised postoperative

scar. Due to the width of the implant the tension and stress on the sutures is greatly diminished in comparison to other methods employed.

The risk of sepsis seems negligible, as the results show, and rarely occurs, especially if the surface epithelium was removed.[8] The use of modern operative technics and antibiotics seem to make Mair's method of hernia repair a safe procedure. The introduction of corium with its rich vascular network, which allows it to become incorporated into the inguinal canal without prejudice to the function of the muscles at the inguinal region, would appear to be an advance over previous methods.

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Clinical Application of a New Plastic Surgical Dressing in 400 Cases

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EVERY surgeon has observed some of the disadvantages of the usual gauze and adhesive tape postoperative dressing, i.e., adhesive burn, bulkiness of gauze, unsatisfactory application to awkardly situated wounds, and inability to see and palpate the wound. Following thoracic and abdominal surgery, overtight taping may cause undesirable restriction of breathing. The sprayable, transparent, polyvinyl plastic dressing, aeroplast,* now makes available a new technic which obviates the undesirable features of ordinary dressings and which, furthermore, is (1) cheaper and easier to apply; (2) has bacteriostatic and bactericidal properties; (3) is non-toxic and non-allergenic; and (4) provides a semi-permeable effect which leads to a dry, clean, primarily healed wound.

Aeroplast was developed in cooperation with the United States Air Force Aero Medical Laboratory for application in the mass treatment of burns, as reported by Choy and Wendt in 1952,[1] and was subsequently used by Choy[2] and Rigler and Adams[3] as the sole dressing in a variety of wounds.

The purpose of this paper is to describe our clinical experiences with aeroplast in a more extensive series of cases than previously reported and to outline some preliminary experimental results with the dressing.

BACTERIOLOGIC STUDIES

In Vitro Tests. *In vitro* studies reported by Choy[2] indicate that aeroplast has a moderate bacteriostatic effect when sprayed on seeded agar plates. Our own *in vitro* tests not only confirm this bacteriostatic effect of aeroplast spray and the impenetrability of the resultant film, but also indicate bactericidal properties as well.

In blood agar and proteose-peptone agar plates that had been thinly sprayed with aeroplast and then incubated at 35°C., no bacterial growth was observed over a period of forty-eight hours. The films of aeroplast were then removed aseptically and the agar plates seeded heavily with Staphylococcus aureus. Control plates were also seeded and all plates then reincubated.

Within twenty-four hours the controls were heavily overgrown with staphylococci. The previously prepared aeroplast plates, on the other hand, remained sterile and even after seventy-two hours' incubation showed only a very scant growth.

Blood agar and proteose-peptone agar plates that had been sprayed with a thin film of aeroplast and then allowed to dry, were individually inoculated with fresh cultures of Staph. aureus, Escherichia coli, Bacillus subtilis and B. proteus. The entire surfaces were purposely streaked with very heavy inoculums. Control plates were set up at the same time and the entire series incubated at 35°C.

At the end of eighteen hours' incubation all control plates were covered by heavy growths of their respective inoculums. On the aeroplast plates, however, growth appeared only at the outer edges of the agar where the aeroplast film had not covered the media.

After thirty-six hours' incubation, growth appeared on all the aeroplast film plates but it had a peculiar distribution. When the aeroplast film was pulled off, the growth was found to be limited to the interstices of the film that

* Supplied by the Aeroplast Corporation, Dayton, Ohio.

had not covered the medium completely. On the control media B. proteus and B. subtilis were characteristically "spreaders." On the aeroplast plates, colonies of these bacteria that had developed in the interstices of the aeroplast film remained intact, and even on further incubation (five days) did not spread onto the agar surfaces previously overlayed by aeroplast. As thus tested, aeroplast is sterile and has a marked bacteriostatic effect on cultures commonly found on the skin. Under certain conditions it appears to have a bactericidal effect.

In Vivo Tests. No *in vivo* experimental bacteriologic studies on aeroplast have previously been reported. Preliminary to extensive clinical use of aeroplast, we were interested in investigating its early and late bacteriostatic and bactericidal action on normal skin (fingers and abdomen) flora, as well as its ability to maintain the sterility of skin (abdomen) previously prepared for operation.

Normal skin of fingers: Under ordinary circumstances of daily work in the laboratory, the second and little finger of each hand was touched for a second to the surface of a sterile blood agar plate. These plates served as controls. Four coats of aeroplast were then applied to the second finger of each of the three subjects. Work was continued as usual and no special care taken when washing hands. After five hours both the aeroplast-covered second finger and the little finger were again touched to the plates. Then the aeroplast film was removed and the second finger again touched to a plate.

Results in all subjects were similar: bacterial colonies on skin beneath the aeroplast dressing were reduced, although colonies increased during the five hours on the outer surface of the film exposed to normal work conditions. Bacterial count on control fingers increased as normally expected. The film withstood the trauma of normal work in the laboratory for the test period of five hours.

Normal skin of abdomen—early effects: In five patients the right lower quadrant of the abdomen was sprayed with aeroplast and the left side was swabbed with sterile buffered saline. The swabs were streaked across Petri plates for culture. Skin was not prepared in any way before application of aeroplast and no attempt was made to smooth out skin folds or crevices. Three hours later a bacterial count was made of the skin under and over the aeroplast film and of the control area. Plating was done in proteose-peptone agar and incubation was at 35°C. for twenty-four and forty-eight hours. The results obtained indicate that aeroplast does effect a marked reduction in bacteria on skin surfaces within three hours. One patient who showed the least marked reduction in colonies had a great many folds in the skin. These had only been bridged by the plastic film but were smoothed out as swab cultures were taken for testing after aeroplast was peeled off.

Long term effects: These tests were repeated in three other patients, except that swabs were taken at intervals of twenty-four, forty-eight and seventy-two hours. Again it was apparent from the bacterial counts that aeroplast does bring about a significant reduction in bacteria on normal skin and that so long as this film is intact the reduction in bacteria is noticeable for as long as seventy-two hours.

In view of the high original bacterial count (over 4,000 colonies) and the very low count (2 to 118 colonies) following aeroplast spray, one must assume it to have bactericidal properties. Cultures showed a significantly lower count as compared to the controls. This would indicate that the aeroplast film was a barrier to the reestablishment of the normal bacterial flora of the skin.

Prepared skin: The protective properties of aeroplast film against bacteria were studied in ten operative cases with fresh wounds. A special technic of applying the dressing, developed by the authors for use in the clinical cases to be described, was used. Control swab cultures were taken from the skin adjacent to the wound preoperatively and postoperatively. Dressings were undisturbed for six to seven days. At the end of this period control swabs were again made from adjacent skin and the aeroplast dressing was peeled back so that swabs could be taken from the surface of the incision. The control cultures served to identify the usual skin flora. All control cultures were made by scrubbing the skin over an area approximately 1 by 2 inches with a sterile swab moistened in sterile buffered saline. Blood agar, proteose-peptone agar, mycophil agar and thioglycolate broth were used for culture media. Particular attention was given to the types of microorganisms isolated since the operative site had been surgically prepared, and, as far as possible, bacteria kept from that area before,

TABLE 1
ANTIBACTERIAL EFFECTS OF AEROPLAST ON SURGICALLY PREPARED SKIN

Patient	Medium Used*	Control Area		Aeroplast-Topper–Dressed Wound Area (6–7 days postoperatively)
		Preoperatively	Postoperatively	
1	1	12 S, 8D‡	11S	Negative
	2	5S†	4S	Negative
	3	Negative	Negative	Negative
	4	Positive	Positive	Positive (48 hr.)
2	1	20 S, 1D	6S, 50D	Negative
	2	7S	Positive	Negative
	3	Negative	Negative	Negative
	4	Positive	Positive	Negative
3	1	3S	10S, 4BS§	Negative
	2	1S	8S	5S
	3	Negative	Negative	Negative
	4	Negative	Positive	Positive
4	1	9S, 40D	8S	5S
	2	12S, 40D	5S	Negative
	3	.....	.....	.....
	4	Positive	Positive	Positive
5	1	Negative	1S	Negative
	2	19S	Negative	Negative
	3	.....	.....	.....
	4	Positive	Negative	Negative
6	1	14S	10S	Negative
	2	4S	14S	2 colonies
	3	.....	.....	.....
	4	Positive	Positive	Positive
7	1	1,200S	Negative	Negative
	2	1,200S	Negative	Negative
	3	.....	.....	.....
	4	Positive	Negative	Negative
8	1	7S, 6D	3S, 2D	Negative
	2	7S, 10D	2S	Negative
	3	.....	.....	.....
	4	Positive	Negative	Negative
9	1	24S	21S	Negative
	2	35S	26S	Negative
	3	.....	.....	.....
	4	Positive	Positive	Negative
10	1	22S	1,000S	Negative
	2	Negative	1,000S	1S (contaminant)
	3	.....	.....	.....
	4	Positive	Positive	Negative

* Media used: 1 = blood agar; 2 = proteose-peptone agar; 3 = mycophil agar; 4 = thioglycolate broth.
† S = staphylococcus.
‡ D = diphtheroids.
§ BS = B. subtilis.

during and after the operation. However, it was important to learn whether the wounded skin site was protected against chance deposition of bacteria.

Results are detailed in Table 1. Aeroplast film dressing kept the wound site sterile for seven days postoperatively in six of the ten cases. Cultures from the other four cases exhibited one to five colonies of Staph. aureus on only one of the media used. Aeroplast film apparently was able to maintain the wounds in a state practically free of bacteria for the seven postoperative days under observation.

MISCELLANEOUS DOG EXPERIMENTS

In an effort to see whether spraying a thin layer of aeroplast on intestines would prevent adhesions, segments of ileum were identified with silk sutures. One segment was then sprayed with a single layer of aeroplast. At operation four weeks later there were several thin adhesions to the sutured areas of the unsprayed portions, but in the sprayed portions there were thick dense adhesions throughout. Apparently aeroplast produced an intense local foreign body reaction. Since these adhesions were strong, it was thought this property of aeroplast might be useful in the strengthening of hernial repair by increasing fibrosis. It was also thought that perhaps the adhesions might be due to the solvent of the plastic rather than the plastic itself. In further experiments aeroplast was sprayed on the surface of a pan of sterile water and the resulting sheet was sutured between the peritoneum and omentum. At operation two months later the sheet of aeroplast had become completely incased in fibrous tissue, resulting from a foreign body reaction.

In another experiment a square section (3 by 3 inches) of the external oblique fascia of the dog was excised and the defect covered in two areas with stainless steel mesh and tantalum wire mesh while a third strip was left uncovered. Half of each strip was sprayed with aeroplast. At operation two months later the defect was completely healed by dense fibrous tissue. No appreciable difference in healing with or without aeroplast was found. Apparently the aeroplast was not toxic in any way when used intraperitoneally and intra-abdominally on these dogs, since they all healed well and remained healthy.

Postoperatively, aeroplast spray was used

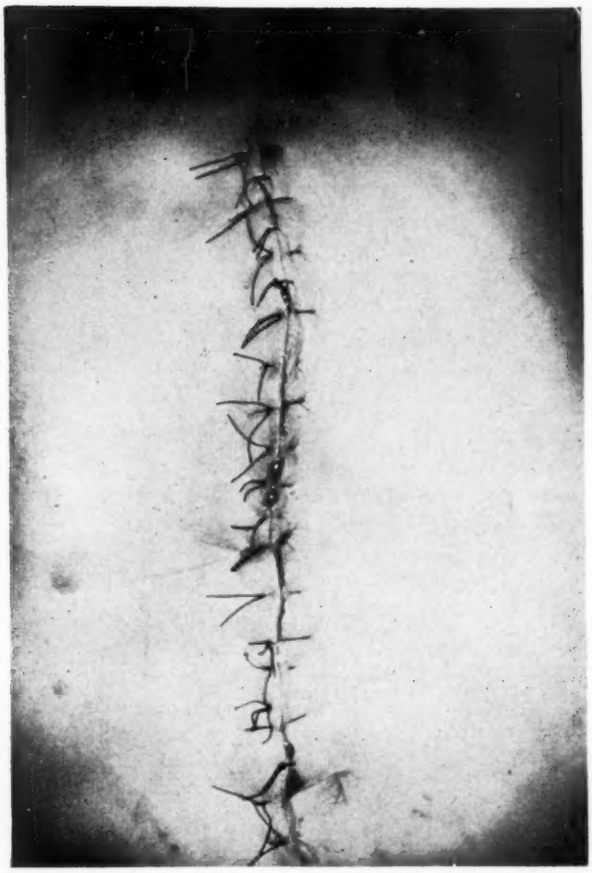

FIG. 1. Aeroplast-topper dressing technic: fresh wound is closed with no unusual precautions for hemostasis. The wound is then sprayed with a thin layer of aeroplast.

FIG. 2. Aeroplast-topper dressing technic: the topper is opened and one side is placed over the freshly sprayed wound and allowed to absorb any blood.

as the sole skin dressing on these dogs. The wounds remained clean and healed by primary union. Used this way, aeroplast is definitely superior to ordinary gauze and adhesive dressings.

CLINICAL STUDIES

Heifetz et al.[4] recognized the disadvantages of the usual gauze and adhesive tape postoperative dressing. They maintained that "if surgical wounds are not dressed, the incision may be observed more frequently. Adhesive tape irritation is avoided and demands on the time and efforts of hospital personnel are lessened. Economy in supplies is also achieved. Inguinal hernia wounds are ideally treated without dressings, especially if incisions are made transversely along the skin lines. Other incisions which may be left uncovered include those employed for an appendectomy, umbilical hernia, cholecystectomy without drainage, exploratory laparotomy, gynecologic surgery and thyroidectomy." However, they list very rigid requirements for closing an incision without a dressing and these are not always possible. They do insist on dressings when surgery is performed under local infiltration anesthesia, for drainage in contaminated wounds which may cause infections, for incisions through scars of previous operations, and when bleeding has not been completely controlled. In addition, rough handling of tissues, closure with catgut, potential or actual dead spaces, splinting and the possibility of trauma preclude omission of a dressing. While it is true that many wounds require little or no dressing, dressings certainly are needed in infants, children and senile patients.

Our experience with operating room personnel has been that they are apt to be confused when several methods of wound dressings are used in consecutive cases. A method which could be used routinely on every type of operative case would undoubtedly be very advan-

FIG. 3. Aeroplast-topper dressing technic: second layer of aeroplast is applied and covered with the remaining gauze. No spray is applied to the outside of the dressing.

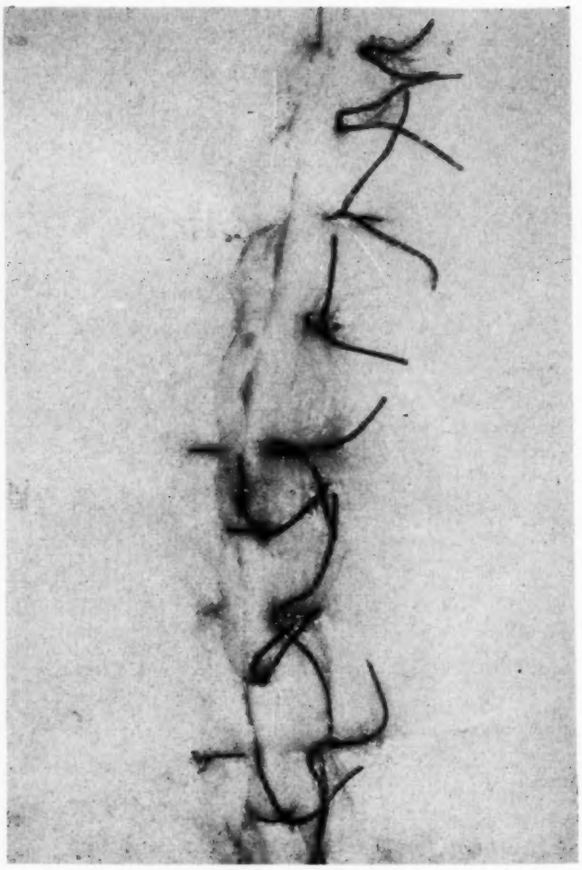

FIG. 4. Close-up of healed wound seven days postoperatively when dressing shown in Figures 1 to 3 was removed.

tageous, especially if it did away with the usual bulky adhesive-gauze dressing while maintaining as far as possible the desirable features of no dressing at all. In our search for such a method, we attempted to duplicate the work of Choy[2] and Rigler and Adams[3] who have used aeroplast spray without gauze as a dressing for a variety of surgical wounds. We soon found, however, that although aeroplast applied by itself was an excellent dressing in many applications, there were other situations in which it would be more useful if combined with a single layer of gauze. Our aeroplast-topper technic has been used in 400 consecutive cases operated on at the Southside Hospital, Bay Shore, and the Central Islip State Hospital, Central Islip, New York.

After closure, with no unusual precautions for hemostasis, all incisions were sprayed with a thin layer of aeroplast and covered with sterile gauze containing cellulose sheets (topper*). (Figs. 1 and 2.) The topper was opened like the covers of a book. What would correspond to the back cover was placed over the freshly sprayed wound and allowed to absorb any blood. When absorption was complete, a second layer of aeroplast was applied over the gauze. This was allowed to dry so that the outer layer of the topper did not become soiled when folded over. If necessary, a third coating of aeroplast can be sprayed between the layers of gauze to make them adhere. No spray should be applied to the outside of the topper. These steps are illustrated in Figures 2 and 3. When a drain was brought out (Figs. 5 and 6), the same technic was used over the wound, the drain being covered separately with gauze and adhesive tape.

The use of this dressing in both hospitals gave us a cross section of every type of surgical

* Made by Johnson & Johnson, New Brunswick, New Jersey.

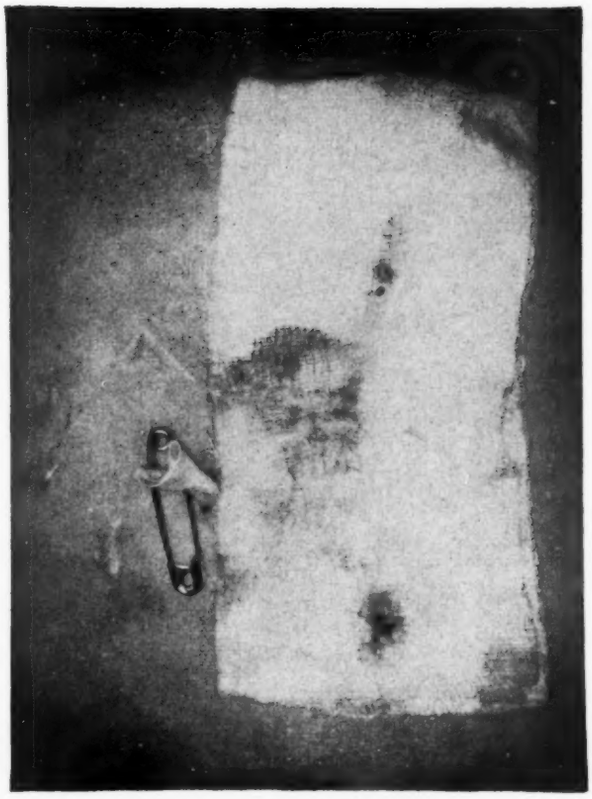

FIG. 5. Aeroplast-topper dressing technic: when a drain is brought out, the incision is dressed as in Figures 2 and 3. The skin around the drain is sprayed to prevent excoriation. The usual gauze and adhesive dressing is then applied.

patient: the private patient and service cases in an emergency hospital and the mental case in an institution. The private patients generally fretted and worried if the aeroplast was applied without gauze because they did not like to see the incision. Later, when a single layer of gauze was used with the aeroplast and a small amount of blood showed through the dressing, they also found this objectionable. The service cases and State Hospital patients, on the other hand, took the uncovered wound or the presence of blood on the dressing in their stride.

Often the application of aeroplast caused an increased oozing of blood in the donor sites of split-thickness skin grafts and around the edges of the ordinary sutured wound. When bleeding was slight, the use of aeroplast without a dressing was satisfactory. When bleeding was appreciable, it formed a coagulum with the sprayed aeroplast which interfered with the formation of an aeroplast film. It was in an effort to overcome this difficulty and to satisfy the occasional

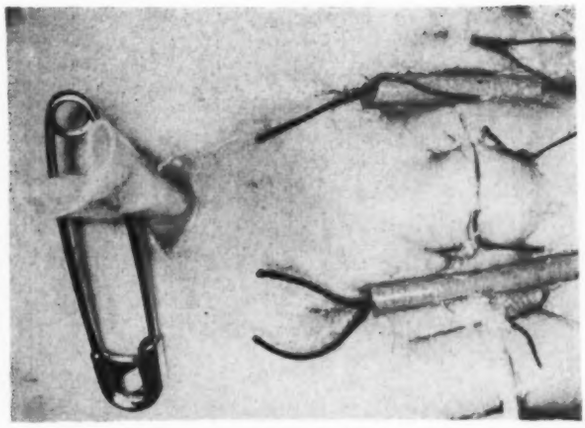

FIG. 6. Postoperative gallbladder wound. Drainage profuse. Note lack of skin excoriation and excellent wound healing.

patient who was disturbed about seeing the wound or blood on the dressing that the aeroplast-topper technic was devised. (Figs. 2 to 6.) Table II gives a breakdown of the types of wounds dressed by this method.

The single topper applied to the wound with two layers of aeroplast was left on the wound

TABLE II

TYPES OF SURGICAL WOUNDS DRESSED WITH AEROPLAST

Wound	Number
Hysterectomy	34
Laparotomy, pelvic	41
Laparotomy, exploratory	5
Cholecystectomy and common duct surgery	35
Herniorrhaphy, inguinal, femoral and ventral	53
Hydrocele and varicocele	4
Saphenous ligation	20
Appendectomy	51
Abdominoperineal surgery	2
Gastric surgery	17
Ramstedt operation	4
Small bowel surgery	2
Colon surgery	6
Pilonidal cyst	6
Mastectomy and segmental breast resection	34
Thyroidectomy	3
Splenectomy	1
Lobotomy	7
Head and neck surgery	9
Perineorrhaphy (skin only)	2
Abrasions and lacerations	6
Skin grafts, donor and recipient	14
Decubitus ulcer	1
Skin tumors, benign	12
Mid-thigh amputation	3
Tendon repair	6
Femur, intramedullary and hip pinning	8
Elbow bursa excision	2
Cesarean operation	9
Total	400

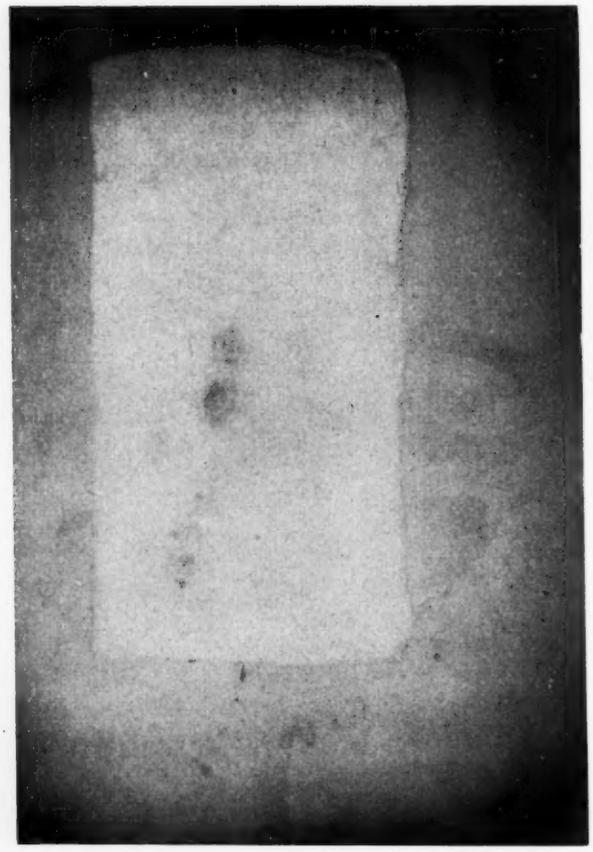

FIG. 7. Aeroplast-topper dressing seven days postoperatively. Dressing is still firmly in place, yet it peels back without pain or difficulty.

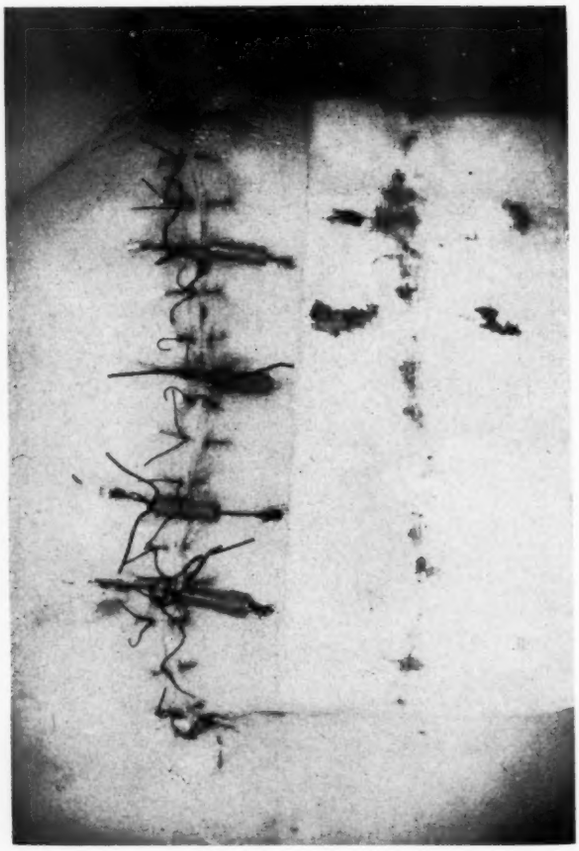

FIG. 8. Illustrates dry, clean appearance of wound and underside of topper seven days postoperatively.

for as long as was necessary, usually five to seven days. During that time the outer layer of gauze became slightly frayed and occasionally the corners peeled back for perhaps 1 inch. (Fig. 7.) The wounds under the dressing remained dry, healed by primary intention and were essentially sterile throughout this period. (Figs. 4 and 8.) At the time of the initial postoperative dressing, the gauze peeled off with very little difficulty. It took with it the layer of aeroplast, making it easier to remove the aeroplast from the wound than in those cases in which the plastic was used alone. By and large the dressings did not stick to the suture except when too heavy a film had been applied. In the occasional case in which this did occur, the suture was held down and a slight pull made on the dressing, thereby separating the two without causing pain. After the original dressing was peeled off, sutures were removed without the need for an antiseptic, since the wounds were found to be practically sterile. The wound was then sprayed and dressed with a single topper or sprayed with aeroplast alone.

At the time of the second dressing, patients experienced a cooling sensation for a few seconds after the aeroplast application. In abrasions, burns or excoriations around draining areas or colostomies, the sensation was one of burning. Although well tolerated at first, this burning sensation became unbearable if dressings had to be repeated at frequent intervals. However, patients with ordinary sutured wounds did not object to the coldness they felt. In the many instances in which aeroplast was applied to the scrotum the sensation of cold, although more marked than on the abdomen, was not uncomfortable enough to warrant the use of a different type of dressing. The advantages of aeroplast dressing in this site are obvious.

Special mention should be made of certain specific uses of aeroplast. The healing of burns after application of aeroplast dressing, as described by Choy,[2] was also observed in our series. The advantage of using an aeroplast-topper dressing over an incision adjacent to a

stab wound with a drain in it or on either side of a drain where it is brought out through the wound was very apparent. Figure 9 shows a ruptured appendiceal abscess wound which was drained and dressed in this manner. The cleanliness of the aeroplast-dressed wound is in marked contrast to the excoriated appearance of the usual wound with purulent drainage. When used in the groin for saphenous vein ligations, aeroplast prevented the maceration often seen in this area. A higher percentage of leg wounds healed by primary union when sprayed with aeroplast and covered with gauze, prior to postoperative application of elastic bandages, than with the ordinary type of dressing. In perineorrhaphy, use of a subcuticular stitch followed by aeroplast spraying allowed healing without the excoriation or irritation often found in wounds in this locality. In pilonidal cyst wounds which were closed with wire, the liberal use of aeroplast kept them completely clean and prevented soiling. In abdominoperineal resections, aeroplast protected the sutured areas from the irritating action of stools and perineal drainage. In the uncommon instances (3 of 400 cases) of a wound with excessive oozing, it has been our practice to apply the aeroplast-topper dressing and cover this for twenty-four hours with a pressure dressing. Skin irritation by the adhesive can be lessened by spraying a single layer of aeroplast onto the skin before applying tape. Since aeroplast conforms to any contour, it is particularly suitable for dressing wounds of the head, neck and axilla. When used on the face, care should be taken to protect the eyes and nostrils. A simple technic for this purpose is to spray aeroplast on the gauze; then, while the gauze is still wet, apply it directly to the wound.

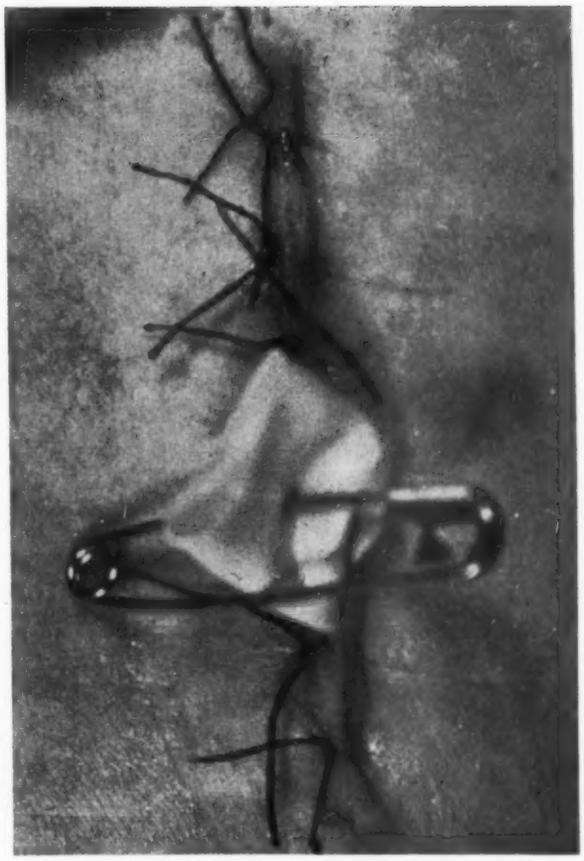

FIG. 9. Illustrates lack of excoriation four days post, operatively in profusely draining ruptured appendix.

SUMMARY

In vitro and *in vivo* bacteriologic tests of the effects of aeroplast on normal and surgically prepared skin indicate that it is both bacteriostatic and bactericidal. Previously reported advantages as to economy and ease of application were confirmed.

A method designed to make the desirable features of aeroplast applicable to every type of operative case, including those in which hemostasis is not complete, was used on 400 consecutive, unselected patients in two hospitals.

Experimental use of the plastic film in dogs to strengthen adhesions in hernia repair suggests further study along these lines.

We believe that aeroplast is a welcome addition to the armamentarium of the surgeon.

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Diverticulitis of the Cecum

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CECAL diverticulitis is a definite yet relatively infrequent lesion in the experience of the average surgeon. Cecal diverticula are estimated to occur in only 1.5 per cent of all patients who have x-ray evidence of colonic diverticula. The presenting symptoms are those of acute appendicitis or the complications of appendicitis. In the 149 cases reported in the literature to date the correct preoperative diagnosis was made in only 6 per cent. In only those cases in which the appendix had been previously removed was any diagnosis other than acute appendicitis made.

Most of the articles in the literature divide diverticula into two types; the congenital or true diverticulum and acquired diverticulum. Most of the diverticula of the cecum that are described are "true" according to the definition which states that "true" diverticula contain all layers of the bowel wall. The acquired diverticulum is thought to arise either from traction by adhesions or because of weakening of the cecal wall following appendectomy.

The preoperative diagnosis of diverticulitis of the cecum is almost impossible to make, since the signs and symptoms are similar to acute appendicitis or one of its complications. The operative differential diagnosis, however, is important. To be differentiated are carcinoma, tuberculosis, non-specific ulcers, actinomycosis and other rare cecal conditions such as regional ileitis, and amebic ulcer. Aside from appendicitis, carcinoma is the most frequent lesion of the cecum. Next in frequency is tuberculosis.

Tuberculosis can be differentiated because, as a rule, the ileum is also involved and small tubercles can be seen on the serosa. The peritoneum is usually thickened and the lymph glands are large and caseous, and adhesions are frequently present.

Actinomycosis of the bowel usually starts in the appendix or cecum. The wall may be greatly thickened, and in later stages small abscesses are formed which may open through sinuses in the abdominal wall, discharging the characteristic sulfur granules.

Carcinoma is the most important, yet the most difficult, lesion to differentiate. Differentiation may be impossible since diverticulitis can present a granulomatous lesion with enlarged hyperplastic mesenteric lymph nodes. This fact explains why 20 per cent of the reported patients with cecal diverticulitis undergo hemicolectomy.

The treatment in the reported cases consisted of either medical therapy, appendectomy, diverticulectomy, appendectomy and diverticulectomy, right colectomy, cecectomy, drainage, simple closure, exteriorization, ileocolostomy with exclusion, cecotomy and appendectomy, ileostomy or appendicostomy. These varied procedures are justifiable because of the rarity of the lesion and its confusion with carcinoma of the cecum.

The treatment advised by most authors and adapted by us consists of the following: For simple diverticulitis without gangrene or rupture, diverticulectomy and appendectomy or appendectomy and medical therapy are employed. For perforation with abscess, drainage is instituted. For extensive cecal cellulitis, gangrene and pseudotumor with ilial obstruc-

tion, iliocecal resection is performed. For cases in which carcinoma cannot be excluded, right colectomy with primary anastomosis as a primary or secondary procedure is performed.

CASE REPORTS

CASE I. A nineteen year old white girl was admitted with a four-day history of pain in the right lower quadrant of the abdomen, chills and diarrhea. There was no history of nausea, vomiting or anorexia, and no urinary or menstrual complaints. On physical examination the patient had a temperature of 100°F.; her abdomen was flat and without scars. There was tenderness with muscle-guarding over the right lower quadrant of the abdomen. No masses or organs were palpable. Peristalsis was hypoactive. Rectal and pelvic examinations revealed no abnormalities. Urinalysis gave normal results; the white blood cell count was 12,500. A diagnosis of acute appendicitis was made and the abdomen was explored through a McBurney incision. The appendix was normal, as were the ovaries and the ileum. The omentum was attached to the cecum where an acutely inflamed solitary diverticulum was located. The omentum was divided and the attached portion sutured to the serosa surrounding the diverticulum. Appendectomy was performed and the abdomen was closed without drainage. The postoperative course was uneventful and the patient was discharged on the eighth hospital day.

CASE II. A thirty-one year old white man was admitted with a two-day history of nausea, vomiting, diarrhea and sharp pain in the right lower quadrant of the abdomen. The past history revealed this to be the sixth similar attack; the previous attacks were not as severe. There were no urinary complaints. Urinalysis gave normal results; the white blood cell count was 9,600. On physical examination the patient's temperature was 101°F. His abdomen was flat and there was marked tenderness and muscle spasm over the right lower quadrant of the abdomen. No masses were present. Peristalsis was absent. Rectal examination confirmed the right-sided tenderness. A diagnosis of ruptured appendicitis was made and the abdomen was explored through a McBurney incision. On entering the peritoneum an inflammatory mass was found which involved a diverticulum on the medial aspect of the cecum. The appendix was normal; no obstruction was present. Appendectomy was performed and the abdomen was closed after a drain was inserted down to the inflammatory mass. The postoperative course was uneventful and the patient was discharged on the thirteenth hospital day.

CASE III. A forty year old white woman was admitted with a two-day history of nausea, vomiting, constipation and pain in the right lower quadrant of the abdomen. There was no history of urinary or menstrual complaints. Urinalysis gave normal results; the white blood cell count was 8,500. On physical examination the patient had a temperature of 100°F. The abdomen was obese and no scars were present. There was tenderness with muscle-guarding over the right lower quadrant of the abdomen. No masses were palpable. Peristalsis was absent. A diagnosis of acute appendicitis was made and the abdomen was explored through a McBurney incision. The appendix was normal. Acute diverticulitis of the cecum was found. There was no evidence of rupture or obstruction. Appendectomy was performed and the abdomen was closed. The patient was treated with antibiotics and was discharged on the fourteenth hospital day after an uneventful recovery.

CASE IV. A sixty-one year old white woman was admitted with a twenty-four-hour history of excruciating pain in the right lower quadrant of the abdomen, nausea and vomiting. There were no urinary or genital complaints. Urinalysis gave normal results; the white blood cell count was 12,000. On physical examination the patient's temperature was 102°F. The abdomen was obese and no scars were present. There was marked tenderness and muscle spasm over the right lower quadrant of the abdomen. No masses were present and no peristalsis could be heard. A diagnosis of ruptured appendicitis was made and the abdomen was explored through a McBurney incision. A perforated cecal diverticulum with localized peritonitis was found. The appendix was normal. The perforation was closed with an omental graft and routine appendectomy was performed. The cecal area was then drained and the abdomen was closed in layers. Antibiotics were given. The patient had a stormy postoperative course but was discharged com-

pletely recovered on the twenty-seventh hospital day.

CASE V. A thirty-two year old white man was admitted with a ten-year history of intermittent abdominal pain primarily in the right lower quadrant. Eight years prior to admission he had undergone abdominal surgery for this complaint. A normal appendix and a mass had been found in the cecum. Without any further procedure the abdomen had been closed and the patient had been informed that he had a tumor of the bowel. A barium enema given prior to this admission revealed the presence of a cecal tumor. A diagnosis of carcinoid of the cecum was made and the patient was admitted for further surgery. The blood cell count and urinalysis were normal. Physical examination revealed no abnormalities. Laparotomy five days after admission revealed a mass in the cecum surrounded by indurated tissue. A right hemicolectomy with an end-to-end anastomosis was performed. Examination of the specimen revealed a thickened and fibrosed cecum. The lumen of the cecum was, to a large extent, obliterated; the mucosa was roughened and hemorrhagic. A diverticulum was found in the center of the endurated mass. The appendix was normal. Microscopic examination confirmed the diagnosis of cecal diverticulitis with pseudotumor formation. The patient made an uneventful recovery and was discharged improved.

CASE VI. A forty-three year old white woman was admitted with a three-day history of pain in the right lower quadrant of the abdomen. There was no nausea, vomiting or intestinal disturbance, and no urinary or menstrual complaints. Urinalysis gave normal results; the white blood cell count was 15,600. On physical examination the patient's temperature was 100°F. The abdomen was flat and no scars were present. There was tenderness with muscle-guarding and rebound tenderness over the right lower quadrant of the abdomen. Peristalsis was active. A diagnosis of acute appendicitis was made and the abdomen was explored. At surgery the appendix was normal. There was a firm, rubbery mass in the cecum with surrounding cellulitis. Cecal resection was performed, as well as a primary ileocolic anastomosis. Examination of the specimen revealed a diverticulum with a surrounding area of induration, edema and inflammation. The postoperative recovery was uneventful.

CASE VII. A forty-five year old white woman was admitted with a thirty-six-hour history of abdominal pain which had become localized in the right lower quadrant. Past history revealed that a hysterectomy and probable appendectomy had been performed three years prior to the present admission. Urinalysis gave normal results; the white blood cell count was 17,500. Physical examination revealed a slightly distended abdomen, generalized tenderness and an extremely tender mass in the right lower quadrant of the abdomen. Peristalsis was absent. A diagnosis was made of abscess in the right lower quadrant of the abdomen, etiology undetermined. The abdomen was opened through a McBurney incision and an abscess was drained. At the base of the abscess a mass was palpated in the posterior wall of the cecum. The abdomen was then closed around drains and antibiotic therapy was started. A barium enema given six days later revealed a diverticulum in the region of the clinically palpable mass. The patient was later discharged with a final diagnosis of diverticulitis with abscess formation and resolution.

CASE VIII. A thirty-six year old white man was admitted with a twelve-hour history of severe pain in the right lower quadrant of the abdomen. There was no nausea, vomiting or intestinal disturbance. Urinalysis gave normal results; the white blood cell count was 11,000. Physical examination revealed excruciating tenderness over McBurney's point, with muscle spasm and rebound tenderness. Peristalsis was hypoactive. A diagnosis of acute appendicitis was made and the abdomen was explored through a McBurney incision. The omentum was found to be adherent to the cecum. The omentum was removed and a perforated diverticulitis of the cecum was found. The perforation had been sealed by the omentum and the tip of the appendix. Appendectomy and diverticulectomy were performed, and the stump of each was inverted. The abdomen was then closed without drainage. Postoperatively the patient was given antibiotics and recovery was uneventful.

CASE IX. A twenty-nine year old Negro woman was admitted with an eighteen-hour

history of epigastric pain radiating to the right lower quadrant of the abdomen, associated with diarrhea. No history of nausea or vomiting was given and there were no urinary or menstrual complaints. Urinalysis gave normal results; the white blood cell count was 8,250. Physical examination revealed tenderness and muscle-guarding in the right lower quadrant of the abdomen. No rebound tenderness was present. The peristalsis was hypoactive. Rectal and pelvic examinations showed no abnormalities. A diagnosis of acute appendicitis was made and the abdomen was explored through a McBurney incision. A solitary diverticulum of the cecum was found. The appendix was normal. Examination of the ovaries and the ileum was normal. Appendectomy was performed and the abdomen was closed without drainage. Antibiotic therapy was started and the patient was discharged on the eighth hospital day.

COMMENTS

Nine cases of diverticulitis of the cecum are presented in which the preoperative diagnosis of acute appendicitis was made in all but two instances. The preoperative diagnoses in these two cases were carcinoid and abscess in the right lower quadrant of the abdomen, etiology undetermined. In the first of these cases, at previous surgery a mass had been found in the cecum, confirmed by x-ray. In the second case, previous appendectomy had been performed during hysterectomy. In both of the cases the final diagnosis was made only during the convalescent period. In all of the cases presented herein the postoperative recovery was uneventful, except in the case in which there was abscess formation. This patient required prolonged hospitalization; however, recovery was complete. Follow-up examinations have revealed no evidence of recurrence in those cases in which the diverticulum was left undisturbed.

In all cases in which the diverticulum is left, appendectomy should be performed and the patient instructed as to the nature of his disease should later differential diagnosis be necessary.

SUMMARY

1. The subject of diverticulitis is presented and its incidence, etiology and differential diagnosis are discussed.

2. Operative diagnosis is stressed and an outline of accepted therapy is given.

3. Nine cases of diverticulitis of the cecum are presented.

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Carcinoid of Meckel's Diverticulum

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MECKEL'S diverticulum occurs in 2 to 3 per cent of anatomic and postmortem dissections.[1,2] In addition to being lined with ileac mucosa, it is the site of ectopic duodenal, colonic mucosa and pancreatic tissue in 25 to 65 per cent of cases.[2,3] This common anomaly is rarely the site of tumor origin. Meckel's diverticula containing benign lesions, such as enterocystoma, adenoma, lipoma and leiomyoma have been described.[13] Malignant tumors, such as spindle-cell sarcoma, leiomyosarcoma, adenocarcinoma, medullary carcinoma and myxosarcoma have been also found within this anatomic anomaly.[10,12,13]

Carcinoid has been found in a Meckel's diverticulum in only eleven instances. The first case was reported in 1922 by Braxton and Kadinsky.[7] This was followed by the case report of Stewart and Taylor.[8] Hertzog and Carlson[9] reported two cases discovered at postmortem examination. Paulter and Scotti,[5] and Ashworth and Wallace[14] each found single cases in their autopsy material. It should be noted that the cases reported by Price,[11] Collins, Collins and Andrews,[12] and Braxton and Kadinsky were instances of carcinoid within an inflamed Meckel's diverticulum. Mrazek. Godwin and Mohardt[4] found one during an appendectomy and another during postmortem examination.

Two cases have been noted at this institution. The first was observed during a postmortem examination and presented the first recorded instance of metastasis.[6] The patient had died from hypertensive cardiovascular disease. The primary tumor, 0.5 cm. in diameter and largely submucosal in the apex of the Meckel's diverticulum, appeared to arise from the Kultschitzky cells at the base of a gland of Lieberkühn. The metastatic nodule, measuring 0.5 cm. in diameter and histologically identical to the primary nodule, was located in the right lobe of the liver.

The following is a report of the second case observed at this institution. Here, as in three of

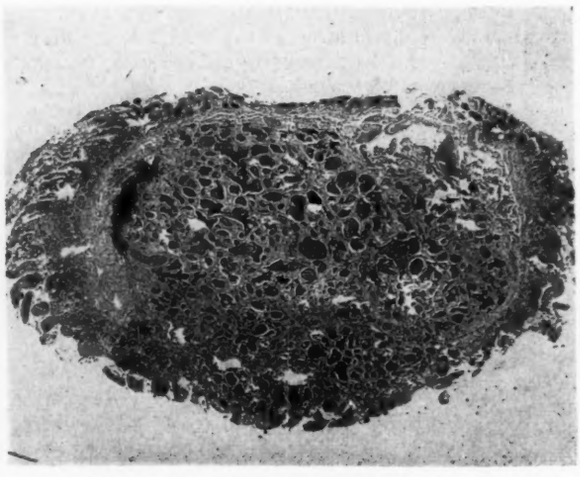

FIG. 1. Shows the carcinoid embedded within the submucosa of Meckel's diverticulum.

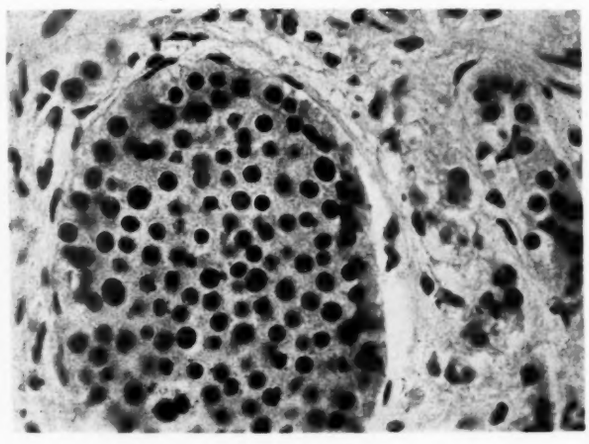

FIG. 2. Shows a high powered magnification of a cluster of carcinoid cells and surrounding accumulation of lymphocytes.

the previously reported cases, the Meckel's diverticulum was the site of diverticulitis as well.

CASE REPORT

G. C. (No. 32077), a fifty-six year old man, was admitted to the Veterans Administration Hospital in Brooklyn on December 11, 1953, with a twenty-four-hour history of progressively severe, non-radiating, aching pain in the right lower quadrant. The patient had had similar but milder episodes of intermittent pain during the previous twenty-six years. Physical findings, localized to the abdomen, revealed diffuse tenderness and moderate spasm, most marked in the right lower quadrant. The white blood count was 12,000 cells per cu. mm. with 81 per cent polymorphonuclear leukocytes; urinalysis was negative. Decubitus and upright flat films of the abdomen showed distended loops of small intestine mainly in the mid-abdomen and toward the right lower quadrant. There were also some localized small air pockets in the right upper quadrant. These were considered to be in the hepatic flexure. Exploration was performed on the day of admission. An acutely inflamed Meckel's diverticulum, 12 inches proximal to the ileocecal valve, was found. The distal portion of the diverticulum was adherent to the mesentery of another loop of ileum, forming a closed loop through which three additional ileal loops had herniated. This latter segment had become moderately cyanotic and distended. The herniated intestine was reduced; segmental ileal resection including the Meckel's diverticulum, with ileoileostomy, and appendectomy were performed. Except for transient ileus during the postoperative period the patient's course was uneventful.

Gross examination of the specimen revealed an inflamed Meckel's diverticulum. A yellow nodule measuring 0.5 cm. in diameter was situated in the submucosa of the apex of the diverticulum. Microscopic examination of the diverticulum revealed chronic and subacute inflammation with a submucosal carcinoid. (Figs. 1, 2 and 3.) The appendix showed periappendicitis.

SUMMARY

Eleven cases of carcinoid of Meckel's diverticulum have been briefly reviewed. The twelfth such case, the fourth in which an associated diverticulitis was noted, has been presented.

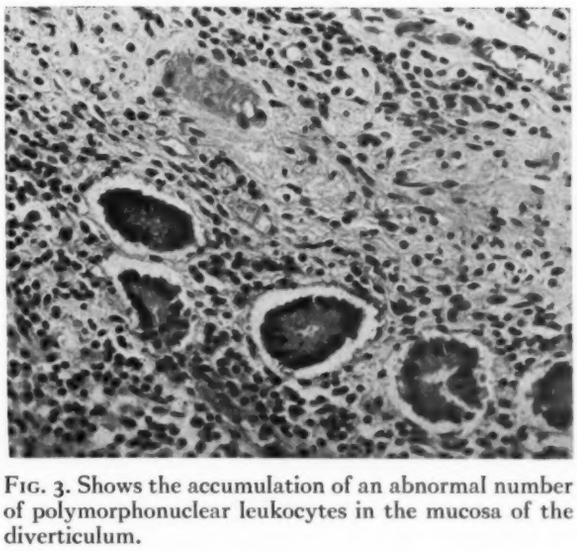

FIG. 3. Shows the accumulation of an abnormal number of polymorphonuclear leukocytes in the mucosa of the diverticulum.

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Late Perineal Evisceration Following Abdominoperineal Resection

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Protrusion of the small bowel through the wound alongside an enterostomy in the immediate postoperative period is not too unusual. This complication, which we have experienced on several occasions, has also been reported by others.[1–4] However, the sudden, spontaneous occurrence of such an incident several years after an abdominoperineal resection ending with a perineal colostomy is most unexpected and rare.

CASE REPORT

A fifty-two year old stout white man was operated upon in December, 1942, for carcinoma of the lower rectum just above the anorectal junction. Abdominoperineal resection with perineal colostomy was performed.

Following the operation a gradually increasing prolapse of the terminal colon developed. This redundant bowel, which had extended 4 inches beyond the skin level, was excised with the actual cautery in April, 1943. The protrusion recurred and slowly increased in size so that ten years later it had descended for approximately 4 inches as a bulky, irritated mass. A more radical excision was recommended at that time (May, 1953).

The corrective operation was performed by opening the perineum and mobilizing 18 inches of the distal colon by a dissection high in the pelvis and lower abdomen. The freed colon was then brought down and the distal segment of 12 inches of this bowel was removed, leaving the new orifice about 2 inches beyond the skin to function as the preternatural anus. The pelvic cavity was loosely packed with gauze and the skin sutured over the gauze. The pelvic space gradually filled in with exudate and granulation but a skin defect failed to epithelize. This area remained as a triangle of granulation tissue with its base of 1½ inches bordering on the colostomy and its apex located 2 inches anteriorly at the base of the scrotum. The apex contained a superficial pus-draining sinus.

The patient was hospitalized one year later because mild diabetes and auricular fibrillation had developed with early cardiac decompensation secondary to mitral stenosis. He also had an active duodenal ulcer. After one week of medical treatment he had improved sufficiently to be discharged. Examination of the colostomy area during this period showed a pronounced perineal bulge from the tip of the coccyx to the scrotum.

On the evening of December 30, 1954, the patient laughed heartily, whereupon he felt a peculiar bursting sensation in the perineal area. He noted a bloody mass hanging between his thighs which he immediately covered with a clean towel. He was taken to the hospital without delay. On admission he appeared comfortable, being neither in pain nor shock. Suspended from the anterior perineal zone was an extrusion of approximately 4 feet of deeply congested but viable small bowel.

In the operating room, under spinal anesthesia, the patient was placed in a moderate prone jack-knife position. Inspection revealed a 2 cm. opening in the perineum through the area of the skin defect. The perineal floor was thin and weak, and consisted of a layer of thickened peritoneum and fibrous tissue covered externally by a layer of granulation tissue. Since these layers were friable and not too resistant, the rent therein was enlarged digitally and the recently extruded small bowel was replaced into the abdominal cavity. A reconstructive reparative effort was made to correct the weak perineum. A satisfactory repair was made by removing excess peritoneum and closing the peritoneal pouch high up in the pelvis. Support-

ing structures were formed by dissecting fibrous flaps from the lateral walls of the pelvis and suturing them in the midline external to the peritoneum. The granulation tissue and sinus were excised, and the skin was undercut and approximated.

The postoperative course was most uneventful. The mild diabetes was controlled with small doses of insulin. No cardiac difficulties arose. The patient received antibiotics as a preventative against infection, and intravenous alimentation for his nutritional needs. By the fifth day his urinary and bowel functions were adequate. The wound healed by primary intention.

A follow-up examination two months later showed the perineum anterior to the perineal anus to be solidly healed, firm and not bulging, whereas that area posterior to the colostomy which did not enter into the repair bulged moderately upon straining.

COMMENT AND SUMMARY

Late evisceration of the small bowel through the perineal area as a complication two years after perineal resection is most uncommon. This mishap in the case presented herein is undoubtedly a consequence of the repeated operations at that site in an obese, diabetic patient whose wound had healed poorly and insecurely.

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Extrusion of a Macerated Fetus and Placenta through the Wound of a Recent Appendectomy

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THE purpose of this paper is to relate a most unusual sequence of events which followed an appendectomy performed upon a woman in her seventh month of pregnancy. A rather thorough review of the literature dealing with abdominal operations upon gravid patients has failed to reveal a similar set of circumstances.

CASE REPORT

N. T., a thirty-two year old white woman, was admitted to the Jewish Hospital of Brooklyn on July 22, 1954, complaining of pain in the abdomen of two days' duration. The illness began with epigastric distress and nausea; localization of the pain to the right lower quadrant of the abdomen occurred twenty-four hours later. The patient had had six previous pregnancies, all of which had terminated in normal deliveries. Her last menstrual period had taken place seven months previously on January 20, 1954. She gave a history of having been a patient in another hospital during the fourth month of pregnancy because of abdominal cramps and vaginal bleeding. An abstract of the record from that institution stated that a diagnosis of intrauterine pregnancy and threatened abortion had been made. The bleeding and cramps subsided spontaneously and she was discharged from the hospital on the fifth day with her pregnancy intact.

Physical examination on the day of admission revealed an acutely ill, obese woman with a uterus the size of a seven-month gestation. Slight tenderness and rebound tenderness were noted in the right lower quadrant of the abdomen. There was no muscle spasm or rigidity and no mass, other than the uterus, could be palpated either on abdominal or rectal examination. Temperature was 99.8°F., pulse was 80 beats per minute, and the blood pressure was 112 systolic and 80 diastolic. The blood count showed 11 gm. hemoglobin; white blood cells, 12,350 per cu. mm.; and polymorphonuclear leukocytes, 86 per cent. Urinalysis was normal.

The admission diagnosis was acute appendicitis in a pregnant woman. The obstetric staff believed that the diagnoses of degenerating fibroids of the uterus or a twisted ovarian cyst had to be considered as secondary possibilities.

The patient was observed for six hours during which time the abdominal pain and tenderness increased. It was decided, therefore, to perform appendectomy. This was accomplished through a McBurney incision, 3 inches long. The operating surgeon stated that the appendix appeared to be acutely inflamed, and it was noted that the tip of the appendix lay upon an enlarged, gravid uterus. No other significant findings were reported except that there was a small amount of clear, yellow fluid within the peritoneal cavity. The pathologic report was "appendix, with periappendicitis."

The patient's postoperative course was accompanied by an elevation in temperature and a non-obstructive jaundice which persisted for twelve days and then subsided spontaneously. On the fifth postoperative day roentgenogram of the abdomen was taken and showed "the skeleton of a fetus in the last trimester of pregnancy in breech presentation." (Fig. 1.) The wound appeared to be healing satisfactorily without evidence of infection. The patient received antibiotic therapy throughout the post-

FIG. 1. Skeleton of fetus seen in breech presentation.

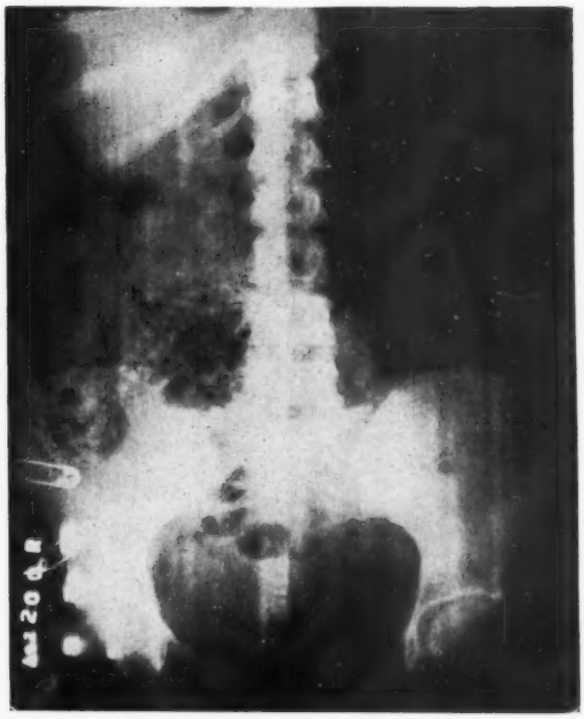

FIG. 2. The dead fetus (as evidenced by gas within the fetal structure) lying in the same position as noted in Figure 1.

operative period. By the fifteenth day the temperature had returned to normal and the patient appeared to be free of symptoms. Accordingly, she was discharged but returned to the hospital the following day because of severe abdominal pain, shaking chills and a temperature rise to 103.5°F.

At the time of readmission she was in a state of shock with blood pressure lowered to 80 systolic and 50 diastolic, a hemoglobin of 8 gm. and a pulse of 100 beats per minute. The abdomen was considerably distended and tympanitic with hypoactive bowel sounds. Six pints of whole blood were administered both to combat the shock and to remedy the anemia which had developed suddenly and had reduced the hemoglobin to 7 gm. On the second day of hospitalization approximately 40 cc. of sanguinopurulent fluid was passed per rectum. The abdomen remained distended and abdominal cramps persisted with rhythmic regularity. There was no evidence, however, of labor and the cervical os remained closed. Flat plate roentgenographic studies of the abdomen were made at this time and revealed a dead fetus lying in the same position as noted on the patient's previous hospital admission. (Fig. 2.)

For the ensuing two weeks, despite intensive combined antibiotic therapy, the patient ran a febrile course with daily elevations of temperature from 100.2 to 103°F. During this period several episodes of sanguinopurulent diarrhea occurred and on one occasion a bloody vaginal discharge was noted.

On August 22, 1954, exactly one month after appendectomy, a tender, warm, fluctuant mass measuring approximately 10 cm. in diameter was palpated beneath the McBurney scar. This was incised two days later and some 300 cc. of brownish, thick, purulent material was evacuated. The right arm of a macerated fetus was seen in the depths of the wound. Several rubber drains were inserted into the wound but no attempt was made to deliver the fetus. Roentgenograms taken at this time showed the fetus to be located in the right lower quadrant of the abdomen, a considerable distance lateral to its previous location. (Fig. 3.)

On the fifth day after incision and drainage of the wound, and almost daily for the next two weeks, various parts of a macerated fetus were extruded through the incision. Considerable pus, showing a mixed infection containing Bacillus proteus, Escherichia coli and B. lactis aerogenes, also drained from the wound. In

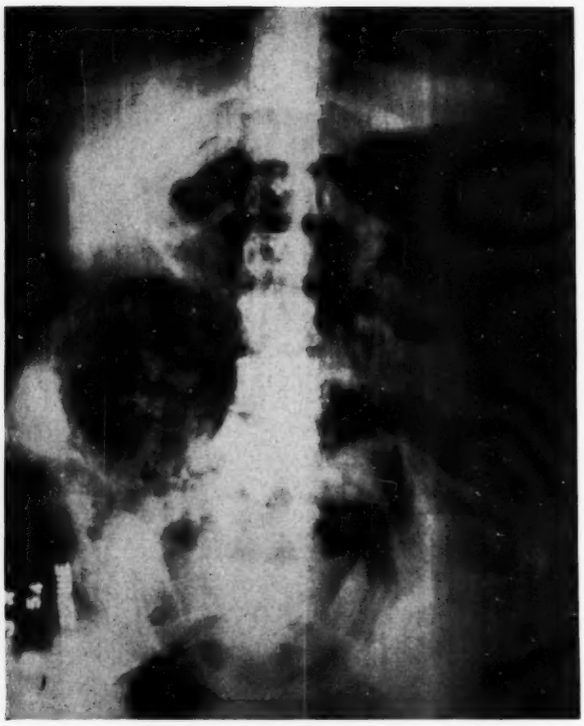

FIG. 3. Fetus is located in the right lower quadrant of the abdomen, a considerable distance lateral to its previous location.

FIG. 5. Hysterogram taken three months after hospital discharge showing a normal uterine cavity.

FIG. 4. Radiopaque dye instilled through abdominal incision and shown entering both uterine cavity and cecum.

view of persistent temperature fluctuations and inadequate drainage, the patient was again taken to the operating room (September 16, 1954), at which time the incision was enlarged and the skull and remaining fetal parts were removed. Despite this procedure the patient continued to run a septic course for another two weeks until a necrotic placenta was spontaneously extruded through the wound. Rapid recovery followed this episode.

On October 14, 1954, instillation of a radiopaque substance into a fistulous opening in the incision showed that the dye entered both the uterine cavity and the cecum. (Fig. 4.) The following day methylene blue was injected into the fistula and was detected in the stools several hours later. However, at no time was fecal material noted in drainage from the wound.

The patient was discharged from the hospital fifty-three days after the incision of the infected McBurney wound. The fistulous opening closed approximately two weeks after the patient left the hospital and she has remained in excellent health to date. A hysterogram, taken on January 27, 1955, revealed a normal uterine cavity with non-visualization of the fallopian tubes. (Fig. 5.)

COMMENTS

The interpretation of the sequence of events in this case must of necessity be somewhat con-

jectural. In retrospect, one can postulate that the abdominal cramps and vaginal bleeding which occurred in the fourth month of pregnancy may have represented either a threatened abortion or the first signs of an impending spontaneous rupture of the uterus. The symptoms which simulated appendicitis in the seventh month of pregnancy were probably caused by further disruption of the uterine wall. The pathologic report did not substantiate the diagnosis of acute appendicitis but showed merely an inflammatory process in the vicinity of the appendix. In view of the findings at operation, namely, the absence of bloody intraperitoneal fluid and the visualization and palpation of an apparently normal, gravid uterus, it can be assumed that the pregnancy was still intrauterine at that time.

The sudden episode of abdominal pain, fever, chills, blood loss and shock which took place fifteen days after appendectomy probably marks the time when the fetus left the confines of the uterine cavity and entered the abdominal cavity. Subsequent roentgenograms, by showing the shift in the position of the fetus (Fig. 3), tend to substantiate this assumption. It is possible that the fistulous tract to the cecum resulted either from a disruption of the appendiceal stump or a perforation of the cecal wall by a bony fragment of the fetus. This would explain the development of bacterial contamination of the fetus and the localized peritonitis.

An alternate consideration, although not very plausible, is that the pregnancy had been abdominal from the beginning and that the fetus was eventually extruded through the surgical incision. However, this assumption seems to be unlikely as repeated pelvic examinations during the fourth and seventh months clearly demonstrated the presence of an intrauterine pregnancy. Furthermore, roentgenograms taken during the seventh month confirm the intrauterine position of the fetus and the injection of a radiopaque substance into the surgical wound shows a direct tract to the uterine cavity. The description of a normal, gravid uterus at appendectomy and the ultimate extrusion of a fairly intact placenta through the abdominal wound also lend credence to the belief that the fetus emerged from its intrauterine position when the uterus ruptured.

SUMMARY

A case is reported in which a seven month old, dead fetus was extruded through the surgical wound of an appendectomy performed one month previously. The patient made a complete recovery.

A Diagnostic Method for Retrocaval Ureter

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JUDGING from the scarcity of reports in the medical literature, retrocaval or circumcaval ureter is a relatively rare condition. In most instances the diagnosis has been made at autopsy or at the operating table. In 1952, Abeshouse and Tankin[1] collected fifty-seven cases from the literature and reported an additional one of their own. Of these, a correct preoperative diagnosis was made in only nineteen cases.

It is apparent that the preoperative diagnosis of retrocaval ureter is infrequently made in spite of the fact that the radiologic picture is supposedly characteristic. The typical pyelographic sign is a medial displacement of the upper half of the ureter toward the midline at the level of the third, fourth or fifth lumbar vertebra. This produces a sickle-shaped or S-shaped curve of the ureter. The distal portion of the ureter lies in a normal position. On lateral or oblique views, the ureter appears closer to the vertebrae and may be anterior to the spine at the level of the third or fourth lumbar vertebra. The kidney may be relatively normal or show varying degrees of hydronephrosis.

It would appear that a more accurate diagnosis of retrocaval ureter could be made if the course of the vena cava was visualized in order to demonstrate its exact relationship to the ureter. In 1949, Duff[2] reported a case of retrocaval ureter diagnosed preoperatively by means of a vena cavagram and retrograde pyelogram performed simultaneously. The vena cava was visualized by injecting diodrast® into the femoral vein through the intact skin. An anteroposterior x-ray film showed the right ureter deviated to the midline beyond the vena cava. No lateral or oblique views were made.

We are reporting a case of retrocaval ureter diagnosed preoperatively and confirmed at operation. A successful end-to-end anastomosis was accomplished after transecting the ureter and replacing it in its normal position. The course of the vena cava was visualized by passing a radiopaque ureteral catheter through the saphenous vein into the vena cava. A retrograde pyelogram was performed and the relationship of the right ureter to the vena cava was demonstrated in the anteroposterior and right oblique views.

CASE REPORT

The patient, a forty-eight year old Negro woman, was admitted to the Cook County Hospital because of recurrent swelling of the ankles. She had had hypertension since her last pregnancy thirteen years previously. At that time a tubal ligation was performed because of toxemia of pregnancy. Since then she had had several episodes of pyelonephritis and ankle edema. On admission, the significant physical findings were a blood pressure of 260 systolic, 140 diastolic and slight pitting edema of the ankles. Examination of the eye grounds revealed slight A. V. nicking. Urinalysis showed a specific gravity of 1.010, 1 plus albumin, and was negative for sugar and acetone. Microscopic examination was negative for formed elements. Urine culture revealed no growth. The non-protein nitrogen was 50 mg. per cent and all other blood chemistry values were normal. Benzodioxane and regetine® studies were normal. An intravenous pyelogram showed poor concentration with inadequate visualization of the right kidney. The left kidney showed normal concentration and configuration.

Cystoscopy and retrograde pyelography were performed. The bladder and ureteral orifices appeared normal. A No. 5 ureteral catheter was passed up each ureter without obstruction. Phenolsulfonphthalein excretion appeared in good concentration from the left kidney in seven minutes and from the right kidney in

FIG. 1. Anteroposterior view of retrograde pyelogram showing deviation of the upper third of the right ureter toward the midline.

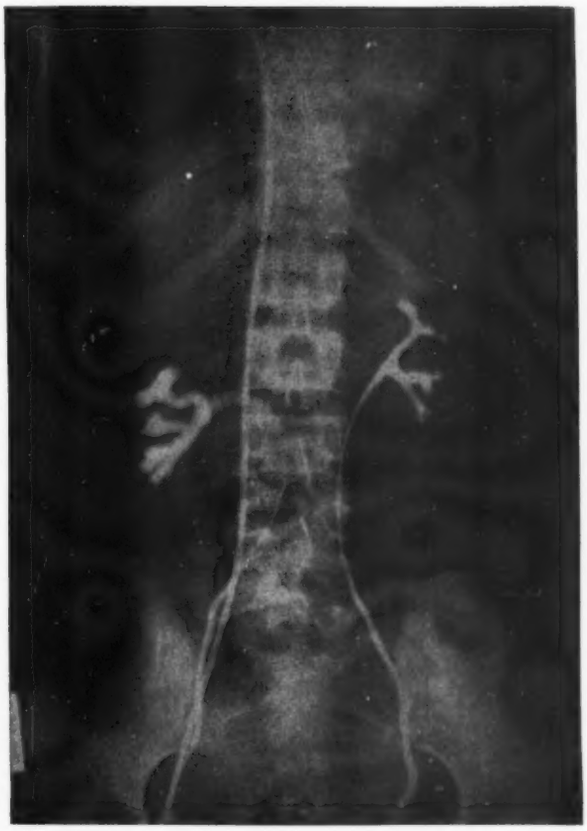

FIG. 2. Anteroposterior view of retrograde pyelogram together with opaque catheter in the vena cava showing upper third of right ureter lying medial to the vena cava.

fifteen minutes. A retrograde pyelogram revealed a normal left kidney and ureter. Some blunting of the calyces of the right kidney was noted and the right ureter was markedly deviated toward the midline along its upper portion, suggesting a retrocaval ureter. (Fig. 1.)

One week later catheterization of the vena cava was performed. First, cystoscopy and ureteral catheterization were done. The ureteral catheters were left indwelling and the cystoscope was removed. The patient's legs were then straightened. Under local infiltration anesthesia, the right superficial saphenous vein was exposed through a small skin incision. The distal end of the exposed vein was ligated with fine silk and just proximal to this a small incision was made. A No. 6F plastic ureteral catheter was passed up into the vena cava. A plain film was taken which showed that the catheters were correctly placed. A retrograde pyelogram was taken and exposures in the anteroposterior and right oblique views were made. The anteroposterior view showed the upper portion of the right ureter deviated medially to the vena cava. (Fig. 2.) The right oblique view demonstrated the right ureter lying posterior to the vena cava a short distance below the pelvis. (Fig. 3.) The catheter in the vena cava was then removed. The saphenous vein was ligated proximal to the site of the insertion of the catheter and the skin was closed. The patient had no reaction to the procedure.

Several days later, exploration of the right kidney was performed through an incision in the right side of the lumbar region under inhalation anesthesia with endotracheal intubation. The kidney appeared grossly normal with an intrarenal pelvis. The ureter was normal in appearance but was seen to course medially and pass under the vena cava about 2 inches below the ureteropelvic junction. It then followed a spiral course behind the vena cava and appeared anterior to the vena cava at a lower level coursing laterally toward its normal position. The ureter was freed for a distance of

FIG. 3. Right oblique view of retrograde pyelogram with opaque catheter in the vena cava showing the upper third of right ureter lying posterior to the vena cava.

FIG. 4. Retrograde pyelogram taken six weeks postoperatively showing normal alignment of right ureter.

approximately 2 inches from the ureteropelvic junction to the vena cava, at which point it was transected in an oblique direction. Distal to this, the portion of the ureter under the vena cava was gently freed and brought out anteriorly and laterally to the vena cava so as to lie in a normal position. The two ends of the cut ureter were approximated without tension over an indwelling No. 6F ureteral catheter using four sutures of No. 0000 catgut passing through the serosa. The proximal end of the catheter was brought out through a wide pyelotomy incision and placed in the posterior angle of the lumbar incision. Penrose drains were placed down to the site of the ureteral anastomosis and the pyelotomy. The wound was closed in layers.

The postoperative course was uneventful. Urinary drainage from the wound was profuse for two weeks at which time the ureteral catheter was removed. After this removal the drainage diminished and the wound was dry by the third week. A retrograde pyelogram six weeks postoperatively revealed normal configuration of the ureter and kidney with the same phenolsulfonphthalein excretion as before surgery. (Fig. 4.) The hypertension remain unchanged.

COMMENTS

Although retrocaval ureter occurs infrequently, it is believed that the diagnosis will be made more often by the use of the technic described herein. If medial deviation of the right ureter is seen on the pyelogram, suggesting the possibility of retrocaval ureter, simultaneous retrograde pyelogram and catheterization of the vena cava should be performed. This method is especially indicated in those cases of minimal or mild hydronephrosis with enough kidney function present to warrant a conservative procedure. By establishing the exact diagnosis preoperatively, a plastic operation can be planned and performed and the ureter replaced in its normal position with an excellent chance of conserving the involved kidney.

The technic of catheterizing the vena cava

is simple and requires no special equipment. The extensive experience in cardiac catheterization would seem to indicate that the procedure is safe and without complications. It would appear that this method is preferable to the direct injection of a radiopaque dye into the vena cava because the danger of thrombosis is eliminated. Another advantage of the catheter method is that the retrograde pyelogram may be taken carefully and unhurriedly and both right oblique and anteroposterior views can be made. With the injection method, the dye is diffused through the vena cava so rapidly that the timing of the retrograde pyelogram must be very exact and only one x-ray exposure can be taken.

The case reported is also of interest in that the medial deviation of the ureter was a gradual one and did not have the typical sharp S-shaped deformity described in the literature. It is possible that some cases with this pyelographic picture are not diagnosed correctly because of the inability to demonstrate accurately the relationship of the displaced ureter to the vena cava. It is hoped that the method described will be of considerable value in the preoperative diagnosis of retrocaval ureter.

SUMMARY

1. A case report of retrocaval ureter which was diagnosed preoperatively and successfully repaired surgically is presented.

2. A method for the accurate diagnosis of retrocaval ureter is described. This consists of a retrograde pyelogram performed with a radiopaque ureteral catheter inserted into the vena cava through the saphenous vein.

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A Case of Severe Melena Due to Primary Carcinoma of the Jejunum

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Carcinoma of the jejunum is a rare pathologic lesion of the gastrointestinal tract. Reports in the literature on the incidence of carcinoma of the jejunum vary considerably. Ewing[6] estimated that 3 per cent of all gastrointestinal carcinomas arise from the small intestine, but this figure appears to be high compared with other reported findings.

Undoubtedly many cases have not been reported, but we believe that the rarity of this condition justifies us in submitting our case and attempting to review the literature.

CASE REPORT

A. F., a seventy year old man, was first seen at the surgical outpatient department of Mayday Hospital on July 8, 1954, complaining of rectal bleeding.

His father had died from laryngeal carcinoma at the age of fifty.

The patient had previously been admitted to this hospital in April, 1951, with carcinoma of the glans penis. Partial amputation of the penis was performed and the lesion was found to be a well differentiated squamous carcinoma with no evidence of metastases. He had been observed at the outpatient department since, without any indication of recurrence.

He had felt well until three to four months before the present complaint when he felt a little "off color," lost his appetite, and occasionally had giddy spells which had become more frequent lately. At about the same time he began to experience occasional bouts of colicky, central abdominal pains lasting fifteen to thirty minutes. These were not severe and were not related to food. One week previously he had lost some dark red blood per rectum and had continued to do so every day since. He gave no history of loss of weight. Examination revealed no abnormal physical findings aside from a moderate degree of pallor.

The possibility of a gastric or colonic neoplasm was considered and the patient was investigated with the following results: hemoglobin, 86 per cent (10.0 gm./100 ml.); red blood count, 3,350,000; white blood count, total 8,700; polymorphonuclears, 88 per cent; lymphocytes, 7 per cent; monocytes, 5 per cent. Barium meal study and follow through showed no evidence of a gastrointestinal lesion. The fractional test meal was normal.

A barium enema was scheduled for July 28th, but on July 27 the patient had a massive rectal hemorrhage, collapsed and was admitted to hospital.

On admission his general condition was good, he was not in pain or in shock. He felt tired and looked extremely pale. His blood pressure was 90/40, pulse 88, regular and of good volume and quality. Hemoglobin was 30 per cent.

Three pints of blood were given immediately and by the next morning his hemoglobin had risen to 52 per cent. Although his blood pressure was still 70/40, he felt and looked well and showed no signs of shock. Three more pints of blood were given that day.

During the next few days he passed a small amount of dark red blood on only one occasion and his condition improved steadily, although the benzedine test of the stools remained positive.

On August 7, 1954, the patient had severe melena and was operated on immediately, the provisional diagnosis being bleeding duodenal ulcer.

The operation was performed through a transverse incision. The stomach and duodenum were normal. However, there was a mass on the jejunum about 8 inches from the duodenojejunal flexure. The jejunum and its

grossly edematous mesentery was attached by multiple adhesions to the transverse colon and mesocolon, forming a mass presenting great difficulty in separation.

As the adhesions were separated, a penetrating ulcer was found in the jejunum, eroding but not perforating the wall of the transverse colon. Appearances suggested that this was a neoplasm of the jejunum. There was no evidence of metastatic spread to either glands or liver.

In order to effect an adequate removal of the lesion, resection of 10 inches of jejunum and 6 inches of transverse colon with end-to-end anastomosis was performed.

Recovery was uneventful, and the patient was discharged fit and well on August 30, 1954. Hemoglobin was 69 per cent; blood pressure, 114/85.

The pathologic report was a constricting "ring" neoplasm with the microscopic appearance of anaplastic carcinoma.

The patient was seen at the outpatient department four weeks later (September 29, 1954). His condition remained satisfactory, and he had had no further symptoms. Hemoglobin was 80 per cent.

On October 21, 1954, he was readmitted with a history of recurrent melena. He was pale but felt well. Hemoglobin was 32 per cent. In spite of repeated blood transfusions, his condition deteriorated and he died six days later.

Autopsy revealed multiple ulcerations of the small intestine 6 inches below the anastomosis, the edge of the ulcers being infiltrated with anaplastic carcinoma similar to that found in the original tumor. No metastases were present.

COMMENTS

In reviewing the literature it becomes clear that carcinoma of the small bowel is a rare lesion, but there is considerable difference of opinion among authors regarding the segment of small bowel most commonly affected by carcinomatous growths. Fraser[8] suggests that carcinoma is more common in the ileum than the jejunum, although the findings in the Mayo Clinic series were to the contrary.[14] Several theories to explain the low incidence of carcinoma of the small bowel have been put forward. Brooksher[4] suggested a multiple causation, the main contributing factors being minimal irritation because of the fluid content of the small bowel, the alkalinity or special inhibitory action of secretions and the absence of any fixed angulations. Mitchell-Heggs[19] suggested that the lack of stasis of the contents of the area may possibly account for the rarity of the lesion.

Swan,[23] in a review of the literature from 1929 to 1945, found sixty-six cases of jejunal cancer. Mayo[14] reported a series of forty cases from 1907 to 1939, while Rankin and Mayo[21] reported 101 cases of malignancy of the small intestine: twenty-four in the duodenum, thirty-nine in the jejunum, thirty in the ileum and the remainder in multiple sites. Medinger[17] reported twelve cases of carcinoma of the jejunum of 1,456 necropsies and 41,000 surgical specimens. Mayo and Nettrour[15] reported that 0.15 per cent of all carcinomas of the gastrointestinal tract were situated in the jejunum, whereas Pridgen, Mayo and Dockerty[20] placed the figure at 1 per cent.

The most common site of carcinoma of the small intestine has not been ascertained. Some authors state that carcinoma occurs "high" in the intestinal tract. (Warren[25] says "high and low with center area free.") Maingot[13] reports four cases of carcinoma of the small intestine of which three were situated in the upper part of the jejunum and one in the lower part of the ileum. These cases support Warren's hypothesis.

The disease is twice as common in males as in females. In Fraser's series of twenty-one cases, thirteen were male and eight female.[8] Neoplasms of the small intestine usually occur during middle age. Ewing[6] reported an average age of 46.5 years. Mayo and Nettrour[16] gave fifty-one years as the average age of incidence for their series. However, Joyce[11] reported a jejunal carcinoma in a twenty-five year old man.

Thomas and Boothroyd[24] consider that the surveys are misleading, owing to the inclusion of tumors which are not carcinomas. Certainly it is difficult to express an opinion on previous surveys, but we have mentioned what we consider to be the most important ones to help in the revision of the literature, keeping in mind the possibility that some may be misleading in confusing carcinoma of the jejunum with other lesions of the small intestine, such as lymphosarcomas.

The symptoms of carcinoma of the jejunum are not stereotyped but vary from little or no

localizing symptoms to those of acute intestinal obstruction.

Prigden et al.[20] suggest the presence of one of three syndromes: (1) anemic syndrome with symptoms related to anemia; (2) the obstructive syndrome; and (3) the perforative syndrome, in which the lesion had perforated the bowel wall and involved the parietal peritoneum and its nerves.

Previously, Mayo[14] said that the two main features are recurrent attacks of intestinal obstruction with intercurrent relief and anemia due to direct loss of blood from the ulcerated regions. Loss of weight is characteristic of carcinoma of the jejunum, this probably being explained by interference with normal bowel function in mobility and absorption. Vomiting is usually intermittent and increases in severity as the obstruction progresses. Pain varies from vague discomfort to severe colic located in the region of the umbilicus and lower quadrant of the abdomen. Melena is also a symptom which can lead one to a diagnosis of ulceration of the duodenum, as in our case.

Emaciation and anemia with cachexia are usually the physical findings in a later stage of carcinoma of the jejunum. A palpable abdominal mass is usually a late finding, and if it is movable it is highly suggestive of carcinoma of the small intestine.[4]

Roentgenographic findings may help in the diagnosis by demonstrating a filling defect at the site of the lesion with a compensatory widening proximal to the obstruction. Delayed emptying is thought to be suggestive of carcinoma of the small intestine. However, Horsley[10] added that avitaminosis, sprue, pellagra and hypoproteinemia may also cause such a finding. A negative roentgenogram does not exclude early cases; in fact, positive roentgenographic findings are rare.

Lingley[12] was able to demonstrate the cavity of a malignant enteric ulcer filled by barium after the remainder of the bowel had emptied. Several methods have been suggested for the detection of tumors of the small intestine. Akerlund[1] suggested screening one hour after the ingestion of a watery barium meal and demonstrated four cases in which the diagnosis was undoubtedly made by the observation of obliteration of rugae, stiffness of a coil, tenderness or a filling defect. Mayo and Nettrour[16] made a correct diagnosis in ten cases of thirty-one studied by this method. Mitchell-Heggs[18] also used the aforementioned method with success. In 1938 Simpson-Smith[22] advised that when obstruction is present but not complete, a Miller-Abbott tube should be passed until it meets the obstruction. The barium injected through the tube then outlines the tumor. The advantage of this method has been proved by Miller and Bell in 1942 in their own cases. However, it is generally accepted that the roentgenographic findings are not very helpful in the diagnosis of carcinoma of the small intestine.

Accurate diagnosis is very difficult. Bowman[3] said that inference of a malignancy of the small bowel may be gained from a careful history, physical examination and laboratory findings, and definite diagnosis only by laparotomy or autopsy. Primary malignant disease of the small intestine must be differentiated from the narrowing due to inflammation. These tumors are, as a rule, of short length (between 4 to 6 cm.) while the inflammatory lesions are longer in length (12 to 15 cm.).

Macroscopically there are three types of carcinomas of the small intestine: (1) the annular constricting adenocarcinoma which resembles the typical cicatrizing growth of the sigmoid colon; (2) the polypoid or papillary tumor which grows into the lumen of the bowel and frequently causes intussusception; and (3) the rounded tumors growing away from the intestinal lumen into the general peritoneal cavity.

Microscopically these tumors are adenocarcinomas, which may be well differentiated or, on the other hand, anaplastic as in our case.

The prognosis is very discouraging whether or not the growth has been removed. Rankin and Mayo[21] reported that not one of their patients lived for more than three years. Medinger[17] reported on twenty-two patients, nineteen of whom were operated upon with 47 per cent mortality. Of those who lived, three were well with no recurrence for periods of eleven years, three years and less than one year, respectively. Babcock[2] gives an operative mortality of 17 per cent and recurrence of 75 per cent. Gatch[9] stated that the results of resection were almost uniformly bad because of the presence of early metastases. Some authors give the mortality rate after operative removal of carcinoma of the small intestine as 30 per cent, and only 10 per cent of cases survive for five years, according to Cameron.[5]

Fraser[8] reported on fifteen patients who were

operated upon for carcinoma of the small intestine. Of these, nine died within fourteen days, increasing the operative mortality to 60 per cent.

SUMMARY

A case of severe melena due to primary carcinoma of the jejunum is presented and the literature on the subject is reviewed.

Acknowledgment: We are indebted to Mr. McElroy, Consultant Surgeon of Mayday Hospital, for permission to publish this case, and to Dr. Dukes, Consultant Pathologist of St. Mark's Hospital, for the pathologic report.

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Jejunojejunogastric Intussusception

GORDON F. MADDING, M.D., *San Mateo, California*, BERNARD F. MCLAUGHLIN, M.D., *Burlingame, California*, AND ROBERT DE RIEMER, M.D., *Berkeley, California*

JEJUNOGASTRIC intussusception is a rare postoperative complication involving the stomach. A recent survey of the problem by Irons and Lipin[1] revealed only ninety-nine published cases to which they added another, making the total 100. The majority of these complications have been recorded in the European literature; only nine instances of this condition have been reported in this country up to the present time.[2] There are a number of reviews of the subject in the literature and the report by Aleman[3] is one of the most comprehensive. He reported a series of seventy cases of jejunogastric intussusception following all forms of gastric operations. This complication has been seen following partial gastrectomy, but the majority of reported cases occurred following gastroenterostomy of the posterior type.

Aleman,[3] in 1948, classified the types of jejunogastric intussusception and this classification has been generally accepted. Class I is an intussusception of the afferent loop of jejunum into the lumen of the stomach and has been referred to as a descending intussusception. Class II, which Aleman found constituted 74 per cent of his series, is an intussusception of the efferent loop and is referred to as the retrograde or ascending type of intussusception. Class III, or the combined type, is relatively rare and consists of a prolapse of both loops through the gastroenterostomy stoma. Irons points out that the intussusception occurring in Classes I and II is usually jejunojejuno intussusception, which in turn, intussuscepts into the gastric lumen. The case we are reporting here in is a Class II variety in which a jejunojejuno intussusception intussuscepted into the stomach proper. Wisoff[4] has depicted the various classes diagrammatically. This complication has been reported as early as the fourth postoperative day[1] and as long after surgery as thirty years.[5] The case we are reporting occurred twenty-six years after gastroenterostomy.

The explanation for retrograde intussusception is not clear but it represents the result of abnormal movements of the intestine. Aleman, in 1923, noticed that the acid contents of the stomach, on reaching the jejunum, produced an irritation which set up antiperistalsis. This in turn may draw the intussuscepted small bowel into the stomach and, in an effort to eject this from the stomach, the reverse peristalsis draws additional small intestine into the stomach through the gastroenterostomy stoma. Oselladore[6] has produced experimentally retrograde gastrogastric invagination in experimental animals by instilling a weak solution of silver nitrate into the stomach. This complication has been reported much more frequently following posterior gastrojejunostomy than following anterior gastrojejunostomy, suggesting an etiologic relationship in the placing of the stoma.

A clinical diagnosis of this condition is not often made for the symptoms in the reported cases are extremely diverse and may vary from a sensation of fullness after meals, frequently associated with nausea, vomiting and moderate colic which may last from one to two hours after eating, to that in which there is a picture of acute upper gastrointestinal obstruction with severe, colicky pains. The physical findings are also variable and may consist of no more than some tenderness in the upper abdominal region. In others, marked abdominal tenderness and board-like rigidity have been demonstrated. A mass is rarely palpable. X-ray studies, using barium meal, are pathognomonic when the small intestine can be demonstrated in the stomach proper. Because of the rarity of this condition, a correct preoperative diagnosis has been made in only three instances in the cases reported.[2]

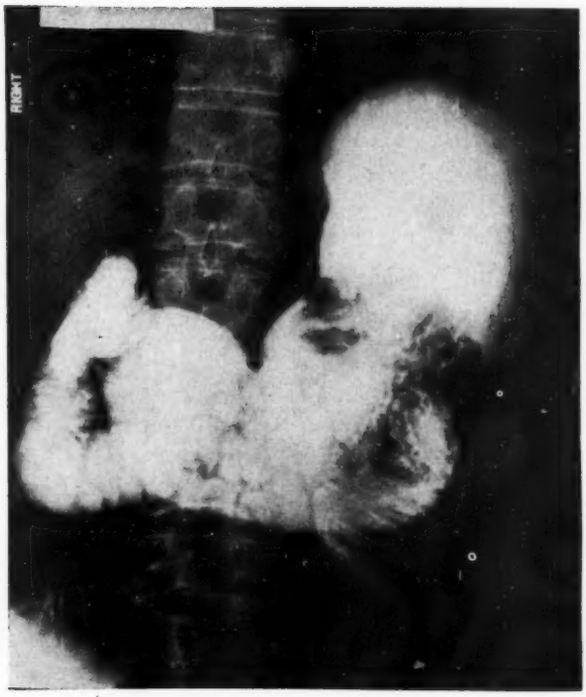

FIG. 1. Preoperative stomach x-ray showing small bowel intussuscepting into the stomach through gastroenterostomy stoma.

FIG. 2. Multiple loops of small intestine within the stomach.

The treatment of jejunojejunogastric intussusception is always surgical. Reduction of the intussusception is usually not difficult and a number of methods have been attempted to prevent recurrences. Fixing of the jejunal loops to each other or to the colon or mesocolon with or without enteroenterostomy has been used successfully. Most often when this condition has followed simple gastroenterostomy, subsequent gastric resection has been performed when the patient's condition permitted. The mortality rate is directly proportional to the time elapsing from the onset of the condition to surgery. Vink[7] has reported that in forty-eight hours the mortality rate is 10 per cent and after another forty-eight hours it rises to 50 per cent.

CASE REPORT

R. L., a sixty year old man, was first seen by one of us (B. F. M.) on April 16, 1955, with the chief complaint of a sudden severe pain in the upper abdomen associated with marked cramping and vomiting. The vomiting was quite intense and, on occasions, small amounts of blood were noted in the vomitus. For the most part, the pain was located above the umbilicus and was non-radiating. This particular episode of abdominal cramps persisted for approximately one hour before medical attention was sought. The patient had a long past history of abdominal distress dating back to childhood when he was known to suffer with chronic abdominal distress manifested by periodic bouts of nausea and vomiting, particularly when he became nervous. The diagnosis of duodenal ulcer was made in 1917 and proved by x-ray. Because of persistent symptoms from the ulcer, the patient had undergone pyloroplasty in 1918. Postoperatively he continued to be troubled with nausea and vomiting associated with a vague upper abdominal distress. In 1929, posterior gastroenterostomy was performed in an attempt to relieve him. His postoperative convalescence again was not good and it was necessary that he avoid all work for a period of six years because of difficulty in eating. From 1929 until the present time, the patient had been hospitalized on numerous occasions for stomach trouble and abdominal distress. In 1947, during one of his hospitalizations, gastroscopy was carried out and no disorder reported. The patient continued to have abdominal distress with nausea and vomiting until the onset of the acute episode on April 16, 1955.

On admission, physical examination revealed

FIG. 3. Postoperative film showing normally functioning gastroduodenostomy following partial gastrectomy of the Billroth 1 type (Von Haberer modification).

an acutely ill, white man, suffering from severe cramping pain in the abdomen. There were no masses palpable in the abdomen, and no evidence of hyperperistalsis could be discerned by auscultation. The abdomen was not distended. Rectal examination was normal as was the remainder of the physical examination. Blood pressure was 136/85, pulse 80 and sinus rhythm was noted. Laboratory findings revealed a normal blood count; urinalysis was essentially negative. Serologic tests gave a negative result.

X-ray studies of the upper gastrointestinal tract were carried out on April 16th and revealed the following: "Apparent intussusception or herniation of the small bowel loops into the stomach through the gastroenterostomy stoma, as described, apparently producing obstruction at the stoma to passage of the barium into the more distal small bowel loops. The small bowel loops within the lumen of the stomach appear moderately dilated with gas." (Figs. 1 and 2.)

Conservative treatment was carried out for approximately twenty-four hours. On April 17th the patient was seen in consultation by one of us (G. F. M.) and a second series of x-ray studies using a small amount of barium revealed the following: "The previously described filling defect in the mid-portion of the stomach, apparently representing herniation or intussusception of the small bowel loops, is again noted, without apparent change from the day before. The mucosal pattern in the stomach itself is quite well demonstrated at this examination and appears to be within normal limits. A small amount of barium passes through the pylorus without delay and into the descending loop of the duodenum." Because of the persistence of the condition, it was believed that surgical exploration was indicated and, accordingly, this was performed by one of us (G. F. M.). Under general anesthesia the abdomen was opened through an upper midline incision. Exploration revealed a retrograde jejunojejunogastric intussusception involving the efferent limb of the gastroenterostomy. There was approximately a 4 to 5 inch segment of intussuscepted jejunum exterior to the stomach, and after some difficulty the entire intussusception was reduced from the stomach.

Twenty-nine inches of jejunum were involved in the jejunojejunogastric intussusception. After this had been completely reduced, the involved segment was markedly thickened and discolored, and in areas it was questionable whether the circulation would return. The most involved area was wrapped in moist warm lap packs, while the gastroenterostomy was taken down. Following this, partial gastrectomy, removing approximately 75 per cent of the stomach, was performed after the method of Billroth 1 (Von Haberer modification). The defect in the posterior mesocolon was closed and because of the questionable nature of the small intestine, resection of approximately 18 inches of jejunum was carried out and end-to-end anastomosis performed. (Fig. 3.)

The pathologic report was "distal segment of stomach with gastroenterostomy stoma showing edema and interstitial hemorrhage. (2) segment of jejunum with mucosal edema, ulceration, and acute inflammation (strangulated through gastroenterostomy stoma)."

The patient's postoperative course was uneventful and oral fluids were started on the third postoperative day. The patient was discharged from the hospital on April 27, 1955. X-ray examination made before the patient was discharged showed a normal functioning

gastroduodenostomy. The patient has been seen in the office postoperatively and states that he has not felt as well in thirty years.

SUMMARY

A case of jejunojejunogastric intussusception occurring twenty-six years after posterior gastroenterostomy has been reported. This patient had the Class II chronic type of intussusception involving the efferent loop as classified by Aleman. In the treatment of the condition, it was necessary to take down the posterior gastroenterostomy after which partial gastrectomy was performed following the method of Billroth I technic (Von Haberer modification). The patient's postoperative course was uneventful.

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Bell and Harding state that the "shock" often present in patients with perforated duodenal or jejunal ulcer is probably due to coexisting "bile peritonitis." They recommend that not only should the site of bile leakage be repaired but also the peritoneal cavity should be irrigated before the abdomen is closed. They also advise the use of dextran to combat the shock. (*Richard A. Leonardo, M.D.*)

Unusual Complications of Hernia Repairs: Large Symptomatic Granulomas

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THE purpose of this paper is to present an unusual complication of hernia which may occasionally arise and present a diagnostic problem. Three cases of large symptomatic granulomas have been encountered at this hospital. They were all matters of interest because of the paucity and intermittency of symptoms and delayed objective findings.

CASE REPORTS

CASE 1. F. F., a sixty-six year old white man, entered the Veterans Administration Hospital in Dayton in July, 1953, with the complaint of a mass in his lower abdomen. Right extra-aponeurotic herniorrhaphy had been performed in September, 1952. One week after operation swelling developed along the line of repair which measured 1½ inches. He stated that at no time had he experienced any discomfort until three to four weeks prior to admission when he noted an increase in the size of the mass and mild pain in the lower abdomen. His history indicated that he had been afebrile and otherwise asymptomatic except for occasional dyspnea and dependent edema.

Upon examination of the patient, a 12 by 12 cm., firm, slightly irregular mass was seen and palpated in the right lower quadrant which extended obliquely upward from the symphysis. Inferior to the mass there was a well healed scar in the right inguinal area. Some observers thought that the mass was either a benign or malignant neoplasm arising from the pubis or fibrous layers of the abdominal wall. Others thought that it represented an infected granuloma. Because the mass was firm, non-tender and immovable to palpation, one could not

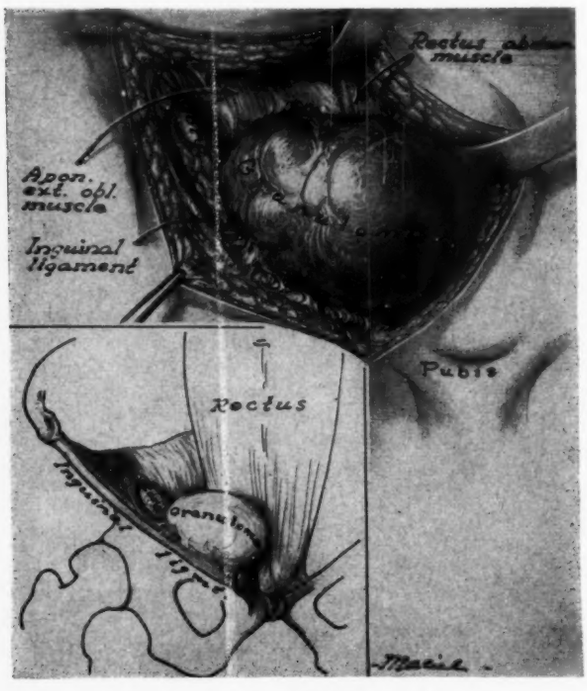

FIG. 1A. Case 1. Drawing showing mass and area involved as seen at surgery prior to excision.

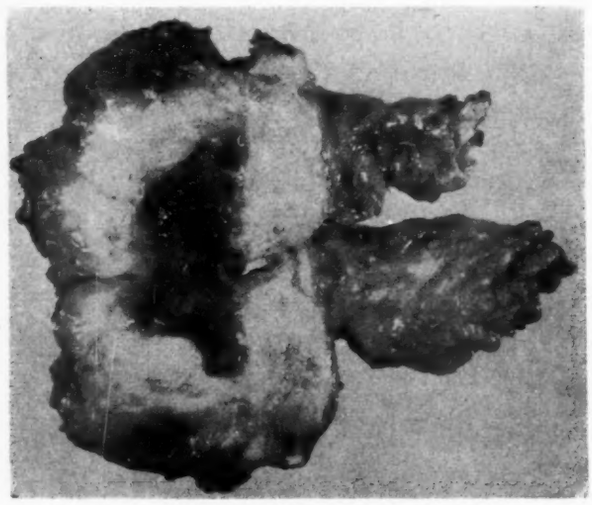

FIG. 1B. Case 1. Surgical specimen.

FIG. 2A. Case II. Cystogram before antibiotic therapy.

FIG. 2B. Case II. Cystogram after antibiotic therapy.

determine exactly which structures were involved. The patient exhibited no manifestation of local infection. Laboratory studies were within normal limits.

Roentgenologic gastrointestinal studies, intravenous pyelograms and films of the pelvis and spine were normal. A biopsy specimen of the mass taken on July 21, 1953, indicated only a proliferation of collagenous fibrous tissue with chronic inflammatory reaction. The clinical impression then was that the tumor represented either a benign fibroma or desmoid. On September 4, 1953, a very large granuloma was removed from the area cephalad to the medial portion of the canal. (Figs. 1A and B.) The center of the mass contained a 2 cm. cavity with a loose silk suture and approximately 10 cc. of pus. The culture proved to be Staphylococcus aureus. The wound was repaired with No. 34 steel wire and healed by primary intention.

CASE II. M. E. P., a thirty-one year old white man, entered this hospital on July 27, 1953, complaining of pain in the right inguinal area with intermittent episodes of fever.

Right extra-aponeurotic herniorrhaphy (Halsted I) had been performed in October, 1951, at this hospital. Subsequently an infection of the wound developed. The latter was treated by multiple incisions and drainage and removal of silk sutures. After the infection had cleared and the wound had healed by secondary intention, the patient complained of recurrent swelling and tenderness in the right lower inguinal and testicular areas. Later he also noted intermittent episodes of low grade fever. He was observed and studied at this hospital where no definite diagnoses could be established. The patient had been given an extensive medical work-up for fever of undetermined origin. The only abnormal findings upon physical examination were a thickened right spermatic cord and a cicatrix in the right inguinal area which were fibrotic processes due to his wound infection. It was also noted at this time that the patient had lost a disability compensation for his service-connected hernia subsequent to the repair and it was thought that his complaints were largely psychogenic in origin. The area about the scar was injected with intracaine® and the patient was discharged after subjective improvement.

The patient re-entered this hospital on July 27, 1953. Examination revealed slight tenderness in the lower pole of the incisional scar and a thickened right spermatic cord. It was noted that the patient experienced slight elevation in rectal temperature (100 to 101°F.) but that routine blood, urine and x-ray studies

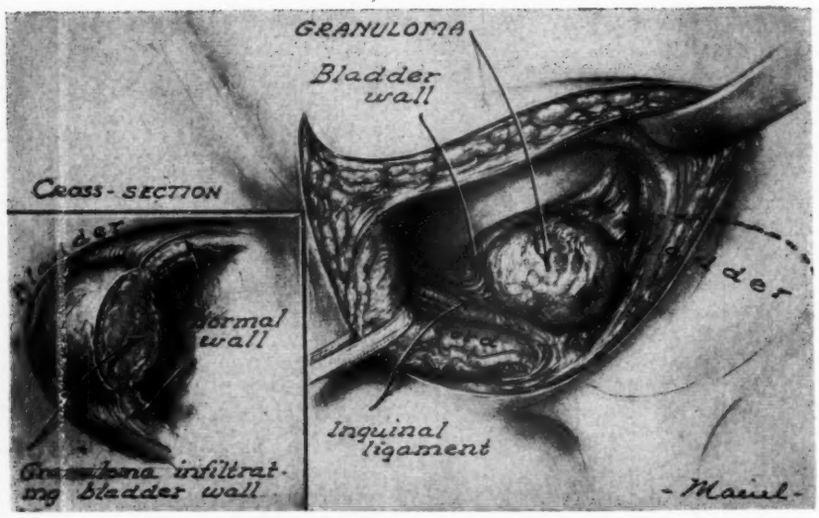

FIG. 2C. Case II. Drawing showing area involved.

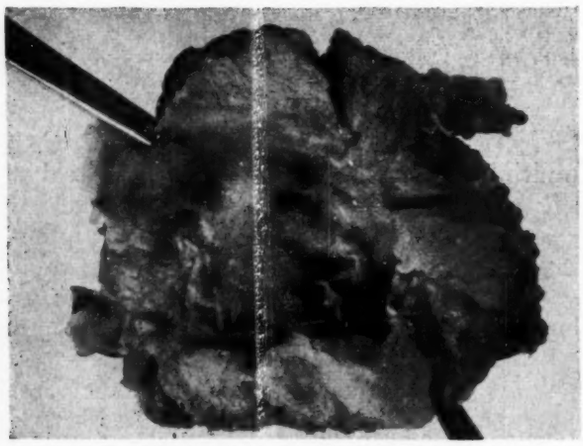

FIG. 2D. Case II. Surgical specimen.

were non-informative. Cystoscopy was performed and cystograms were obtained which revealed an extrinsic mass causing a pressure defect in the right bladder wall. (Fig. 2A.) The patient was thought to have a low grade inflammatory process in this area and was treated with erythromycin, 200 mg. four times a day, and bedrest for one month. He remained afebrile and his symptoms became minimal. Repeat cystograms and cystoscopy were obtained and the findings were only those of mild inflammation of the right upper bladder wall with no evidence of extrinsic pressure as previously noted. (Fig. 2B.) However, after antibiotic therapy was discontinued he again became symptomatic.

The patient's wound was explored on September 23, 1953, and a large granuloma was found deep in the inguinal area involving the right wall and dome of the bladder. (Fig. 2C.) Upon sectioning the specimen, which had been removed *in toto*, a central cavity was encountered filled with pus which contained a black silk ligature. (Fig. 2D.) The pathologic report corroborated the clinical impression of a granuloma. The wound was again closed with No. 34 steel ligatures. An uneventful recovery was made and upon discharge the patient was afebrile and asymptomatic.

CASE III. R. I. R. (117 775), a twenty-seven year old white man, had undergone left inguinal herniorrhaphy at Camp Campbell, Kentucky, in 1943. The wound healed *per primam* and the patient's postoperative course had been uneventful. Five years later the patient was referred to this hospital by a veterans administration physician for examination and evaluation of his operative procedure. A mass, 9 cm. in diameter, was noted immediately beneath the scar in the skin. It was firm, nontender and immovable. The patient was asymptomatic except for mild discomfort at times. There was no disability in walking or exercising. Laboratory and radiographic studies were of no aid. A clinical diagnosis of granuloma was made and the mass was removed on August 4, 1948. Pathologic studies again revealed a laminated granuloma with a central cavity containing a black silk suture and a small quantity of pus. The culture revealed Staph. aureus. The patient's recovery was uneventful and he was discharged.

COMMENTS

The etiology of these large symptomatic granulomas is unknown. They apparently develop around a small nidus of infection associated with a suture in a portion of the wound. In order to attain their large size, there seems to be a progressive stimulation of fibrous connective tissue which develops in laminated layers about a small infected silk suture. In none of these patients was there a tendency to form keloids.

The incidence of such complications is extremely low. In the last twenty-five years at this hospital there have been three cases of approximately 7,500 herniorrhaphies in which large symptomatic granulomas have developed. Since the over-all complication rate following herniorrhaphies is well below 2 per cent at this hospital, these large granulomas are rare occurrences. Small granulomas have been noted in various surgical wounds.

Our interest in the aforementioned three cases has been stimulated by their atypical behavior. The granulomas progress slowly in size and cause pain and discomfort due to pressure on surrounding nerves and viscera. Because of the histories and firmness to palpation, the differential diagnosis has included various soft tissue, cartilaginous and bony tumors.

In the literature, references are occasionally made to small, 1 to 3 cm. granulomas which arise following the use of now absorbable suture material. In 1947 Orr reported five cases of granulomatous masses which developed after the use of silk or cotton in clean wounds. These lesions appeared below the incisional scar, were all palpable and varied between 2 and 10 cm. in diameter. Leithauser has reported the formation of granulomas following the use of nylon as late as ten months after its use. Shambaugh recorded one case in which a secondary abscess developed after the use of silk five months after complete healing of the wound. I believe that these three large granulomas deserve attention due to their symptomatology, progressive increase in size, low incidence and the problem presented in differential diagnoses.

SUMMARY AND CONCLUSIONS

1. Three large symptomatic granulomas have been encountered at this hospital in the last twenty-five years.

2. The incidence of granulomas is one in 2,500 herniorrhaphies. They have not been found in other surgical wounds. The etiology is unknown.

3. Granulomas are atypical because of their slow progressive increase in size and subsequent symptoms. They may occur either superficially or deep in a wound and may or may not be evident by physical examination.

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BOOK REVIEW

A Stereoscopic Atlas of Human Anatomy. By David L. Bassett, M.D., Associate Professor of Anatomy, Stanford University, Stanford, Calif. Color photographs by William B. Gruber. **Section 1, The Central Nervous System.** Twenty-one pages of introduction; 238 pages of keyed drawings, 238 pages of description and keys; 22 index pages; 34 View-Master reels (each with 7 subjects on Kodachrome film); and View-Master stereoscope with light attachment. Portland, 1952. Sawyer's Inc. *Tentative price* $22.50. **Section 2, Head and Neck.** Five volumes; keyed drawings with description and keys; 50 View-Master reels (each with 7 subjects on Kodachrome film); and View-Master stereoscope with light attachment. Portland. Sawyer's Inc. *Tentative price* $22.50.

This comprises the first two sections of an extensive Atlas of Anatomy that will eventually comprise seven sections. Sections dealing with the upper extremity, thorax, abdomen, pelvis and lower extremity, respectively, are now in preparation.

On right hand pages are line drawings of anatomic parts, with prominent landmarks numbered. On left hand pages are listed the legends corresponding to the numbered or keyed illustrations. The dissections show they have been done by a professional endowed with great skill. These have been photographed in color and are magnificent, to say the least. The work is the result of successful collaboration between author, photographer and medical artist.

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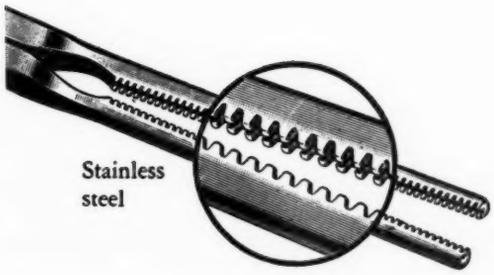

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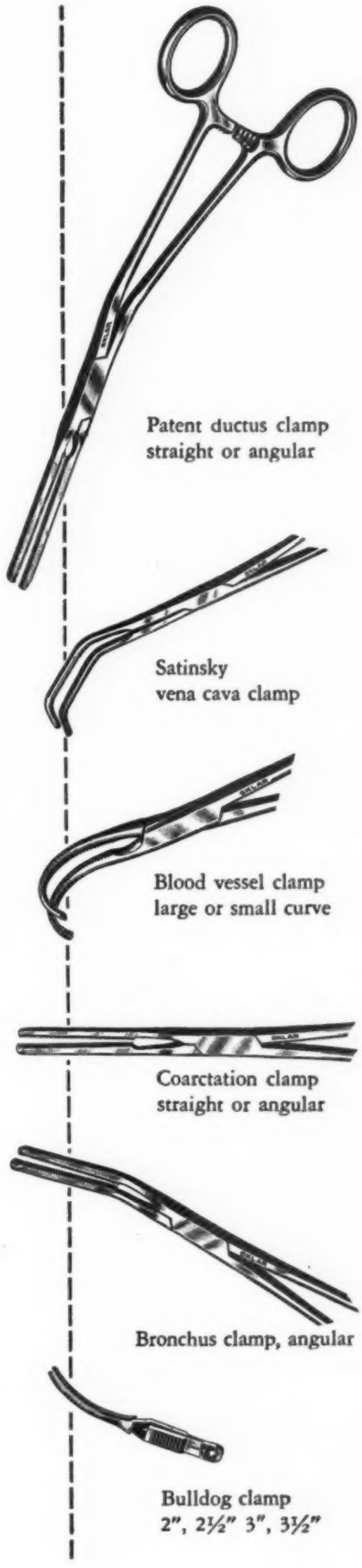

Patent ductus clamp
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Satinsky
vena cava clamp

Blood vessel clamp
large or small curve

Coarctation clamp
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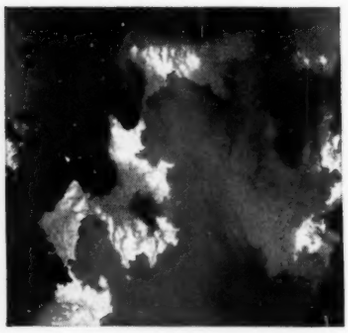
over

inflammation



Many patients with inflammatory lesions respond dramatically when VARIDASE is given intragluteally. Action is similar to VARIDASE applied locally, but results are much more swift and hitherto unattainable areas may be treated by the intramuscular route.

When employed in this manner, VARIDASE lyses the "limiting membrane" of leukocytes and fibrin which is thrown up about an inflamed or infected area. Thus, liquefaction and resorption of the contained exudate is made possible. In case infection is present, or feared, an antibiotic such as ACHROMYCIN* Tetracycline should be administered concomitantly to prevent the development of generalized sepsis.

Recent investigation has extended the list of indications for intramuscular VARIDASE therapy to include abscesses, burns, cellulitis, edema, epididymitis, hemarthrosis, sinusitis, lymphangitis, lymphadenitis, and thrombophlebitis with or without superimposed infection.

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Administration: INTRAMUSCULAR, deep in the upper, outer quadrant of the buttock

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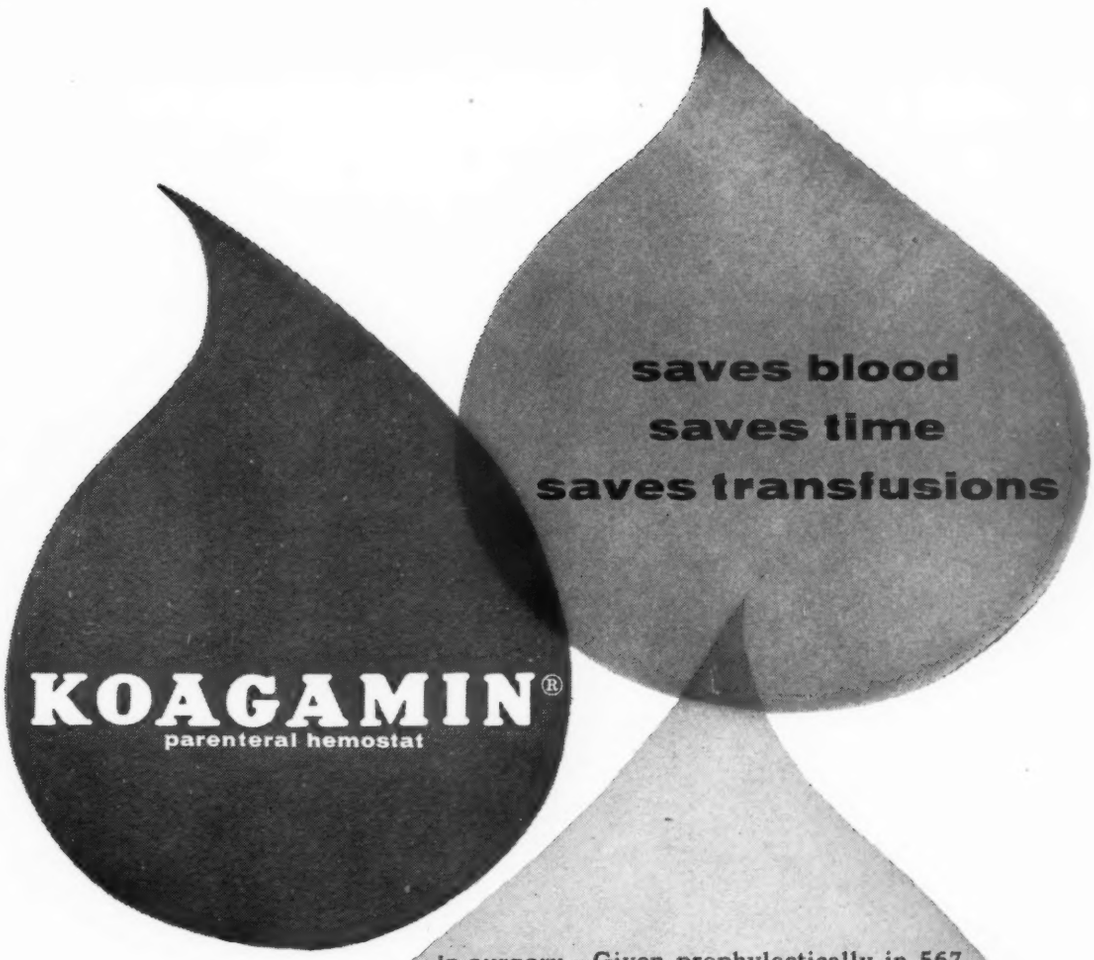

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*Joseph, M.: Am. J. Surg. *87*:905, 1954.

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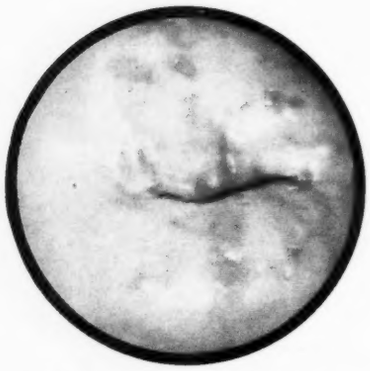
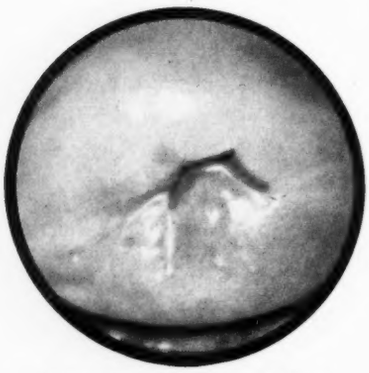


2 weeks post-cauterization



3 weeks post-cauterization, healing nearly complete

PHOTOGRAPHS BY SCHWARTZ, J.: AM. J. OBST. 63:579, 1952.

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after electrosurgery for cervicitis in cancer prevention

There is a "... wealth of statistical proof that chronic cervicitis is an important predisposing factor in the development of cervical carcinoma ..."[1]:

No. cases cervicitis	Treatment	Developed cancer	Followed
1,000	wide conization	0	2-14 years
1,408	cauterization	0	3 years
2,985	cauterization or diathermy	0	10 years
1,150	cauterization	0	not stated[1]

Electrosurgery is treatment of choice in long-standing cervicitis.[2] When purulent discharge and inflammation are present, treat with FURACIN Vaginal Suppositories before electrocautery.[3] Afterward, use them to prevent infection and accelerate healing.[4]

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1. Crossen, R. J.: Diseases of Women, St. Louis, the C. V. Mosby Company, 1953, p. 509. 2. Novak, E., and Novak, E. R.: Textbook of Gynecology, Baltimore, The Williams and Wilkins Company, 1952, p. 220. 3. Patterson, J. F., Jr.: North Carolina M. J. 17:165, 1956. 4. Schwartz, J.: Am. J. Obst. 63:579, 1952. 5. Schwartz, J., and Nardiello, V.: Am. J. Obst. 65:1069, 1953.

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---

1. Odel, H. M.: Nutrition in Cardiovascular Disease, in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, Dietotherapy, Philadelphia, Lea & Febiger, 1955, p. 709.
2. Berg, C. P.: Utilization of Protein, J. Agr. & Food Chem. *3*:575 (July) 1955.
3. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 6, Baltimore, Williams & Wilkins, 1955, p. 638.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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*Kinney, Joseph J.: J. M. Soc. New Jersey *53*:128 (March) 1956.
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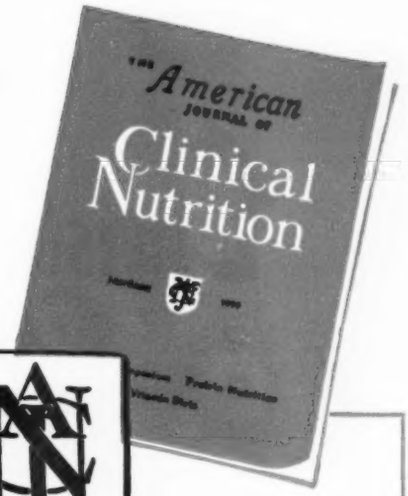

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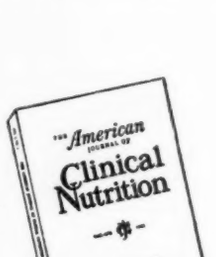

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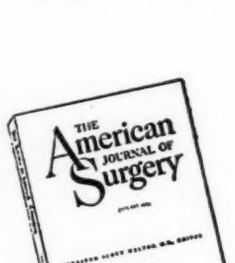

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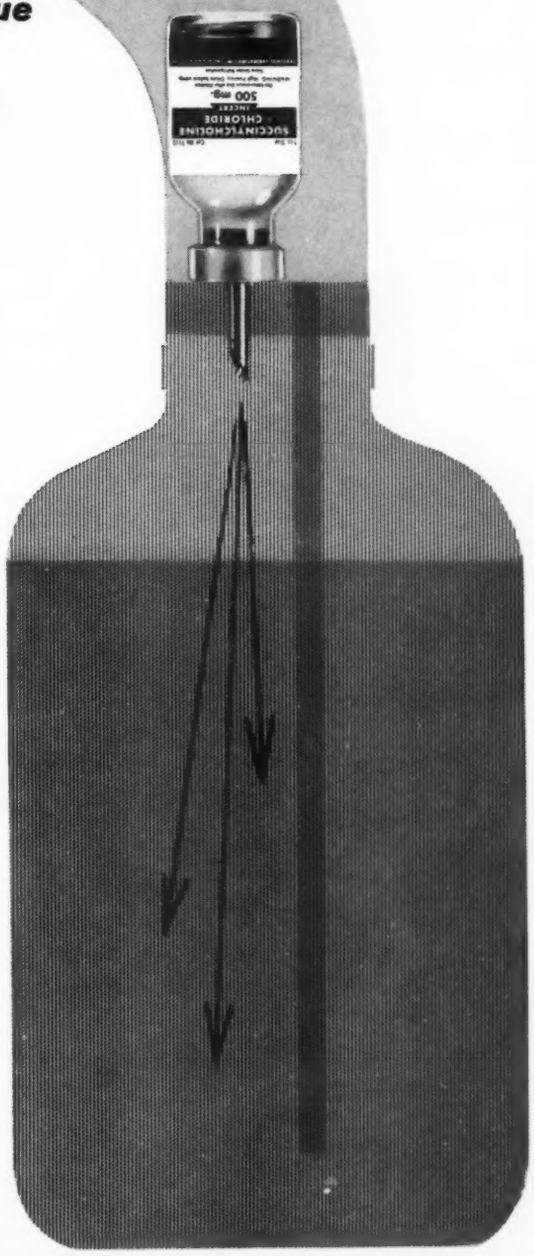

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References: 1. Elman, R., and Cannon, P. R.: in Clinical Nutrition, Jolliffe, N., et al., eds., New York, Paul B. Hoeber, Inc., 1950, p. 183. 2. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Washington, D. C., National Academy of Sciences, National Research Council, Publication 234, 1952.

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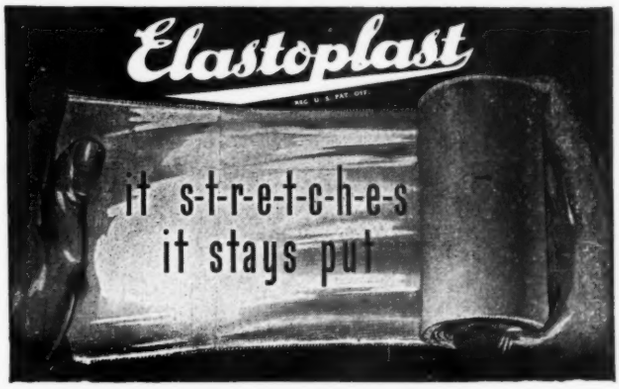

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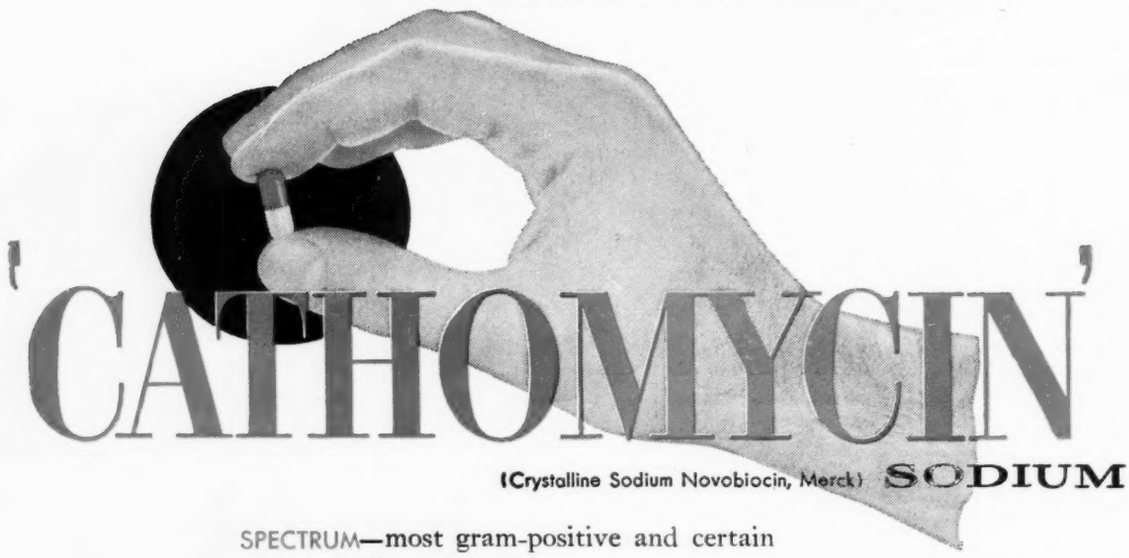

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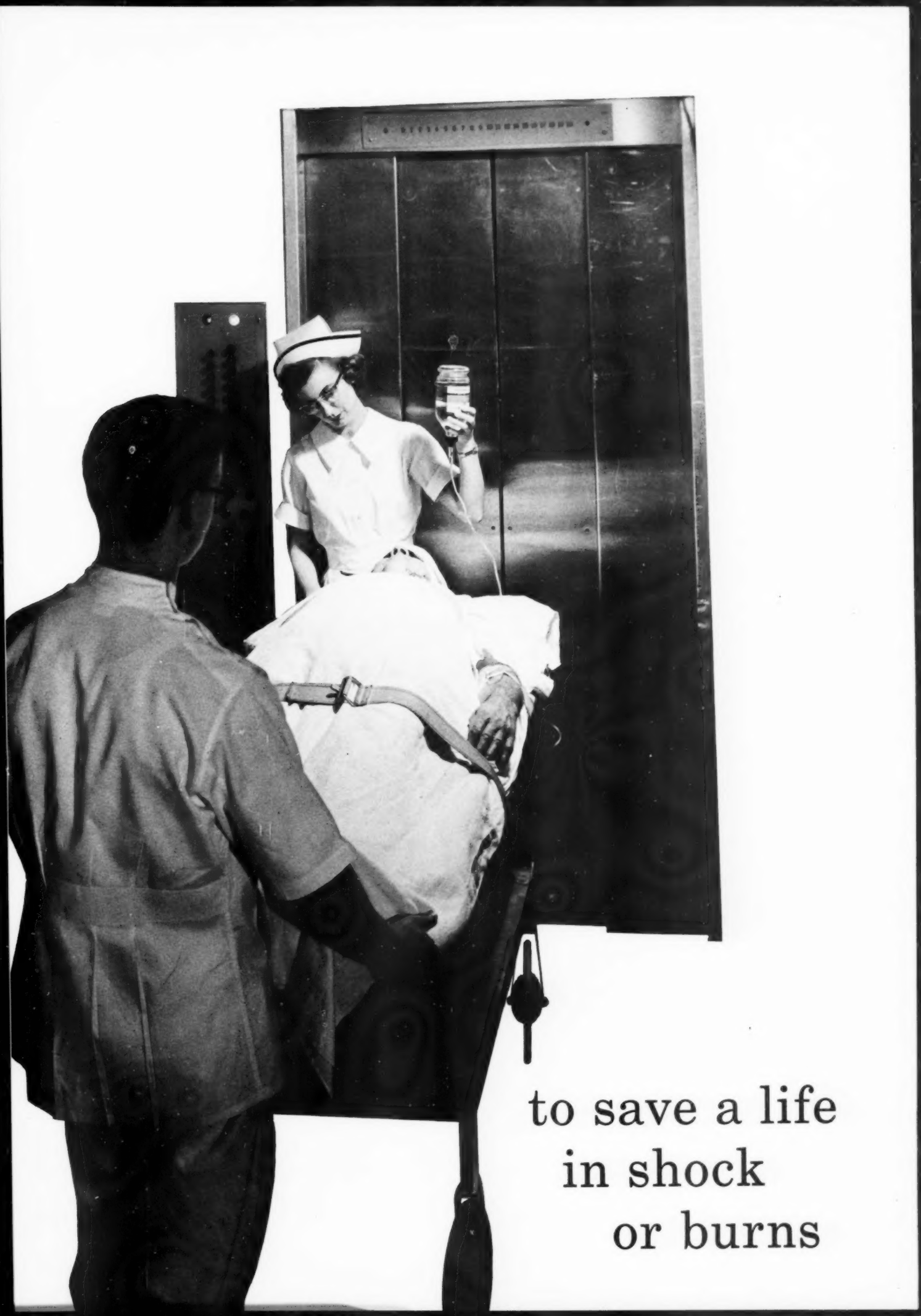

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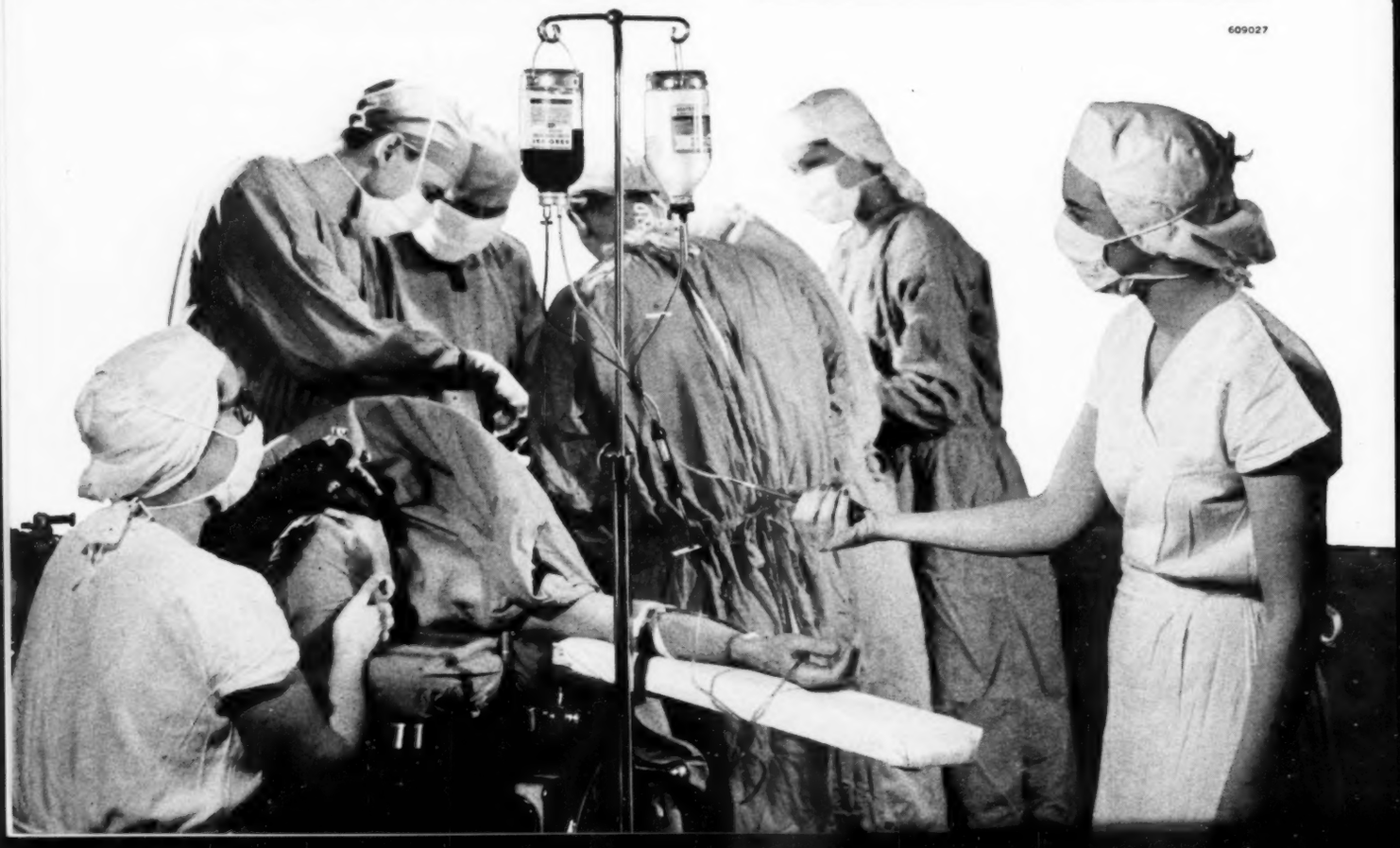

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NOTES AND QUOTES

THE HAWTHORNE SURGICAL SOCIETY, of the Graduate School of Medicine, University of Pennsylvania will hold its annual meeting on October 10, 1956, in San Francisco on the occasion of the American College of Surgeons' convention. Arrangements for cocktails and dinner at the St. Francis Yacht Club are being made by Dr. Everett H. Dickinson, 490 Post Street, San Francisco 2, California. Reservations and checks for $10 per person should be forwarded to Dr. Dickinson. The Alumni of the Surgical classes, Graduate School of Medicine, University of Pennsylvania, are invited to attend.

The George P. Pilling and Son Company of Philadelphia has introduced Stetson endoscopic cleaning brushes. Designed for Dr. John B. Stetson of Ann Arbor, Michigan, this new cleaning brush set consists of a metal flushing stem and three sizes of brushes. The brushes are made of permanently attached nylon bristles and screw securely into one end of the stem threaded for this purpose. The stem is a rigid metal tube, to the handle of which a water hose may be connected; water exit holes are located at the distal end of the tube. The brushes permit a constant flushing action during mechanical cleansing. They are suitable for all types of bronchoscopes and esophagoscopes, Flagg and McGill tubes of metal, woven or plastic material and related instruments.

A BROADER attack upon the "unknown" in man's major diseases will be started immediately by Veterans Administration.

V. A. said an enlarged medical research program will be conducted with the $10,000,000 that Congress appropriated for fiscal year 1957, beginning July 1, 1956—$4,300,000 more than was appropriated last year.

Most of the increased medical research will be concentrated in four areas of major diseases: (1) mental, nervous and brain diseases (neuropsychiatric); (2) heart and artery diseases (cardiovascular); (3) cancer and leukemia; and (4) problems of aging (geriatrics).

"Mankind Against the Killers," by James Hemming, with foreword by Dr. Brock Chisholm, former Director-General of the World Health Organization, has been published by Longmans Green and Co., London, New York and Toronto.

Microbes ignore both national frontiers and social barriers, and the health of each of us is therefore dependent upon the health of all. But, as Dr. Chisholm points out in his foreword, no agency which works across many frontiers can succeed without full public support based on knowledge and understanding of its work. This book helps to supply both.

Mr. Hemming has succeeded in explaining with simplicity and clarity how minute parasites work upon the human body, and shows how the impact of some diseases has shaped the course of history.

CANCER (malignant neoplasms) ranks second only to heart disease as a cause of death in middle life, that is, in the age range forty-five to sixty-four years. In 1955 there were more than 90,000 cancer deaths at these ages in the United States; they accounted for about one-fourth of the total mortality in this age group and for nearly two-fifths of the deaths from cancer at all ages combined. It is estimated that one of every eight persons reaching age forty-five will develop cancer by age sixty-five.

Currently, about 230,000 new cases of cancer occur in our country each year among persons in the age range forty-five to sixty-four; 125,000, or little more than half, are among women. These estimates are based upon the findings in the cancer morbidity survey made in ten major cities in 1947 to 1948. At the time of that study, there was about one case of cancer in every 200 white women at ages forty-five to forty-nine, the proportion increasing to one in every ninety at ages sixty to sixty-four. Among white men the corresponding rise in prevalence of the disease with advance in age was much more rapid—from one case in every 350 to one in every eighty. This morbidity study indicated that in middle life the most common sites of cancer among white women were the breast and uterus, and among white men the skin and lung.

Surgeons are now using scissors that do not get dull. The developers of the nationally selling Ochsner diamond jaw needle holders have now perfected, with the aid of Dr. Alton Ochsner,

CONTINUED ON PAGE 52

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NOTES AND QUOTES

Chief Surgeon, Tulane University, a line of surgical scissors with tungsten-carbide cutting edges. This material is the hardest metal made by man and it is permanently built into the cutting blade of the scissors. It offers extraordinary resistance to wear and maintains sharpness for extremely long periods of time. Ochsner diamond edge scissors can be supplied now through your surgical dealer or direct from Snowden-Pencer Corporation, P.O. Box 186, Los Gatos, California.

How closed-circuit TV has cut by 20 to 30 per cent the time formerly needed to perform heart catheterization operations was reported recently by the Dage Television Division, Thompson Products, Inc., Michigan City, Indiana, manufacturer of closed-circuit television equipment.

Conceived by Dr. F. Mason Sones, Jr., Director of the Heart Catheterization Laboratory and Dr. C. Robert Hughes, Chairman of the Department of Radiology at the Cleveland Clinic, Cleveland, Ohio, the Dage closed-circuit TV system has in some cases cut more than one hour from the usual three-hour operation.

Dr. Sones explained that the TV system makes it possible for the doctor to study the heart in a well lighted room during the operation which formerly was performed in complete darkness.

The TV camera is focused on a small fluoroscopic image of the heart, made bright enough for practical television photography by an electronic device known as a fluoroscopic image amplifier. The TV camera transmits the image to a large television screen where it may be easily studied by all doctors and nurses of the team performing the operation.

By means of additional television monitors connected to the camera in a closed-circuit, the televised picture of the heart may be viewed in another room prepared to permit observation by consulting physicians and instruction of students.

The degree of contrast present in the bright full sized image on the television screen may be electronically controlled, permitting better visualization of detailed structures than was possible before by conventional fluoroscopy.

The combined use of television photography and fluoroscopic image amplification reduces the amount of x-ray required for study of structures within the body to less than two-thirds of that which was required for conventional fluoroscopy in a completely darkened room.

The Eighth Annual Postgraduate Assembly of the Endocrine Society, in cooperation with The University of Texas Postgraduate School of Medicine and The University of Texas M. D. Anderson Hospital and Tumor Institute, will be held October 22–27, 1956, at the Texas Medical Center in Houston. Further information may be secured from: Office of the Dean, The University of Texas, Postgraduate School of Medicine, Texas Medical Center, Houston 25, Texas.

SERA-VAC, a major advance in blood bottle design, has been released by Baxter Laboratories, Inc., originator of the closed system of blood collection and infusion. A sterile, vacuum pilot tube inside the blood bottle provides four primary advantages over conventional equipment: (1) prevents errors because the internal pilot tube cannot be mislabeled, interchanged, lost or broken; (2) saves technician time by eliminating labeling and taping of a pilot tube to the blood bottle; (3) is easier to store and rotate for daily inspection; (4) improves clot retraction because the internal pilot tube, warmed by blood around it, cools slower than tubes taped to the bottle.

Opportunely with respect to the June tradition, the Metropolitan Life Insurance Company's statisticians report a marked trend toward earlier marriages in the United States. Currently about half the men who eventually marry do so before age twenty-three; for women the median age at first marriage is about twenty years.

The total number of married people in the country's population has reached a record high of 81¾ million, which compares with 75 million in 1950, and 60¼ million in 1940.

At present almost 70 per cent of the population at ages fifteen and over is married, whereas for the decades prior to World War II the proportion was at most little more than 60 per cent, according to the statisticians' report, which is based largely on Bureau of the Census data. The increase in

CONTINUED ON PAGE 54

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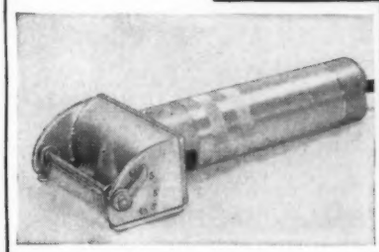

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NOTES AND QUOTES

the married proportion of the population has been considerably more since 1940 than in the preceding half-century.

THE INTERNAL REVENUE SERVICE recently published Rule 52-261 which covers deductions for medical expenses. The ruling defines what constitutes medical expenses in sixteen cases. An important case is No. 10, having to do with air conditioning. The pertinent part of the ruling follows:

10. Air conditioning device. Inquiries have been made as to the deductibility of the cost of an air conditioning device which has been installed in a room of the taxpayer's residence for the purpose of effecting relief from an allergy or for relieving difficulty in breathing due to a heart condition. It is held that the cost of an air conditioning device, plus the operating expenses, less any resale or salvage value, constitute an allowable deduction as a medical expense subject to prescribed limitations, provided that the need for it is substantiated by evidence submitted to show that the device is used primarily for the alleviation of a person's illness and provided further that the device does not become a permanent part of the dwelling and may be removed to other quarters.

Dr. Benjamin M. Duggar, the discoverer of the golden antibiotic, aureomycin, was recently honored by the University of Wisconsin with an honorary Doctor of Science degree.

To the eighty-four year old scientist, the award for his achievement in the field of antibiotic research was doubly rewarding, in that he was Professor of Plant Physiology and Economic Botany at the University for more than sixteen years.

Dr. Duggar, a consulting scientist to the Research Division, American Cyanamid Company at Lederle Laboratories, Pearl River, New York, discovered aureomycin chlortetracycline, the antibiotic proved effective against a wide range of diseases in 1948. Since that time, the versatile antibiotic has found application in a number of industries. In addition to treating diseases in man and animals, the golden drug is added to animal feeds to promote growth and health. Small quantities of it are added to huge tanks of chill water to preserve the shelf life of poultry; and tests indicate it will prove a valuable preservative for fish, for beef and for other perishable foods.

As the first of the so-called broad-spectrum antibiotics, aureomycin paved the way for the development of achromycin tetracycline, now widely used by physicians throughout the world to treat infectious diseases.

THE AMERICAN PSYCHOSOMATIC SOCIETY will hold its Fourteenth Annual Meeting at Chalfonte-Haddon Hall in Atlantic City on May 4 and 5, 1957. The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than December 1, 1956. The time allotted for presentation of each paper will be twenty minutes.

Abstracts, in sextuplicate, should be submitted for the Program Committee's consideration, to the Chairman, 551 Madison Avenue, New York 22, New York.

Organization of the Commission on Professional and Hospital Activities, Inc., was announced in Chicago recently by the American College of Surgeons, American Hospital Association, American College of Physicians and the Southwestern Michigan Hospital Council. The organizations established the Commission to conduct a medical statistical service that will help hospitals simplify medical records and analyze records more effectively for improvement of medical and administrative practices.

The Commission has received a grant of $260,000 from the W. K. Kellogg Foundation, Battle Creek, Michigan, to support the program for three years, after which it is expected the service may be continued on a self-sustaining basis.

Commenting on the new Commission and its services, Dr. Paul R. Hawley, Director of the American College of Surgeons, and President of the Commission, said: "The principal objective of the new Commission is to help hospitals and their medical staffs do a better job of caring for patients by the provision of accurate data and comparative analyses and studies relating to patient care."

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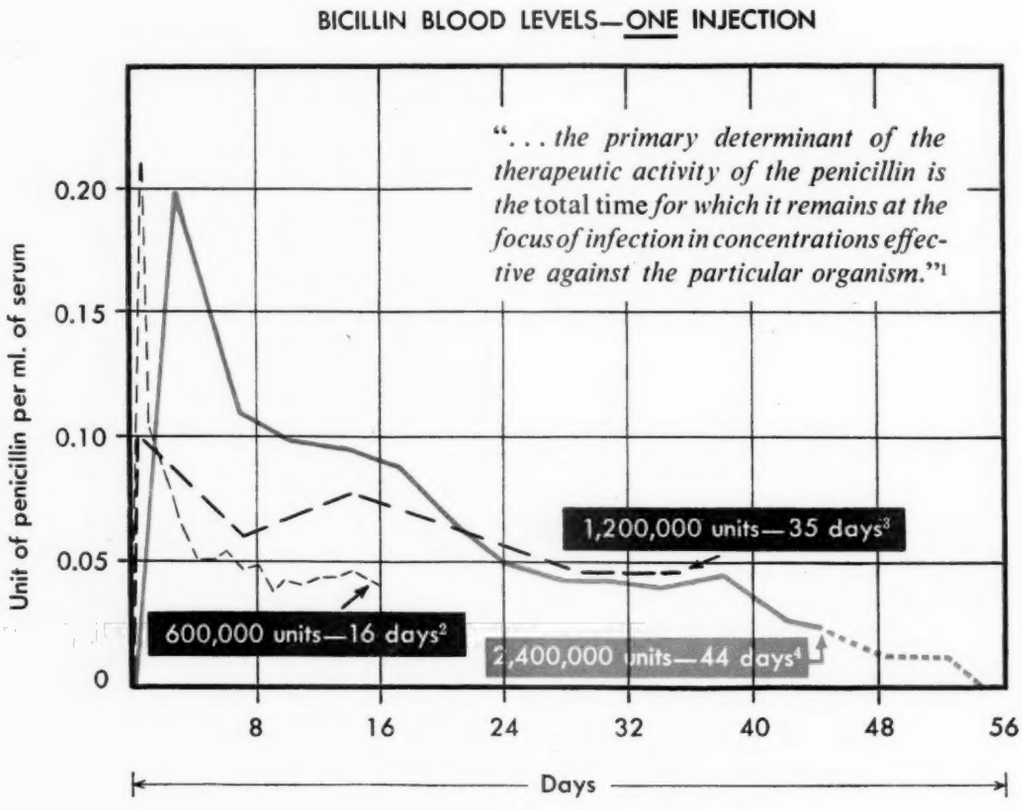

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